

ABANT İZZET BAYSAL UNIVERSITY
THE GRADUATE SCHOOL OF NATURAL AND APPLIED
SCIENCES



THE REACTIONS OF SOME MÜNCHNONE DERIVATIVES
WITH ELECTRON-DEFICIENT ALKENES

DOCTOR OF PHILOSOPHY

HAMZA KARAKUŞ

BOLU, MAY 2015

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APPROVAL OF THE THESIS

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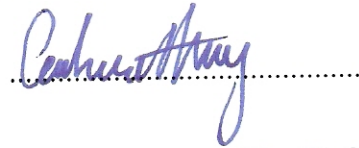
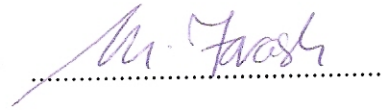
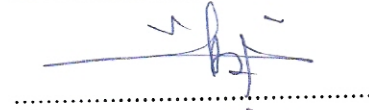
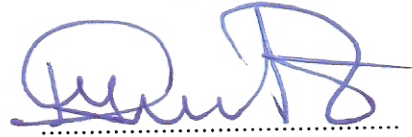
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DECLARATION

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HAMZA KARAKUŞ

ABSTRACT

THE REACTIONS OF SOME MÜNCHNONE DERIVATIVES WITH ELECTRON-DEFICIENT ALKENES

PHD THESIS

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ABANT İZZET BAYSAL UNIVERSITY GRADUATE SCHOOL OF
NATURAL AND APPLIED SCIENCES

DEPARTMENT OF CHEMISTRY

(SUPERVISOR: PROF. DR. YAŞAR DÜRÜST)

202 PAGES

BOLU, MAY 2015

This thesis general describes a variety of reactions of 1,3-oxazolium-5-oxides, commonly known as Münchnones which are a special class of azomethine ylides with electron-deficient dipolarophilic reagents. In this regard, a series of pyrroles, *N*-benzoyl benzamides, *p*-substituted benzoic acids and *N*-acyl ureas have been obtained. These compounds are important heterocycles, widely present in natural and many pharmaceutical compounds. There are many synthetic methods to prepare pyrrole derivatives in the literature. Among them, 1,3-dipolar cycloaddition reaction of Münchnones with alkynes and alkenes are versatile. The purpose of this dissertation is to study the reactions of mesoionic Münchnone derivatives with electron deficient alkenes. The outcomes of these compounds were discussed in three parts;

In the first part, the cycloaddition reaction of *in situ* generated Münchnones from *N*-acyl amino acids with benzo[*b*]thiophene 1,1-dioxide is described. The accompanying deoxygenation of sulfone moiety gave rise to the benzothiophene fused pyrrole derivatives. In order to rationalize the entire reaction, the transformation of sulfide into sulfone group which is the anticipated product was carried out by means of *m*-chloroperbenzoic acid oxidation.

The second part of this work was involved in the synthesis of (*E*)-1-(*N*,4-dimethylbenzamido)-1-(4-fluorophenyl)prop-1-en-2-yl acetate, 4-aryl-*N*-methyl-*N*-(4-substitutedbenzoyl)benzamides and *p*-substituted benzoic acids by the reaction of *in situ* generated Münchnones from 2-(4-substitutedphenyl)-2-(*N*-methyl-*N*-*p*-substitutedbenzamido)acetic acids with acetic anhydride in the presence of 2-nitromethylene thiazolidine. A plausible Dakin-West type mechanisms for these reactions were proposed.

The last part of this thesis, a novel efficient route leading to *N*-acyl urea derivatives was described by the reaction between Münchnone precursors with carbodiimides in the presence of a base.

KEYWORDS:

Münchnone, 1,3-dipolar cycloaddition, acetic anhydride, Dakin-West, carbodiimide, urea

ÖZET

BAZI MÜNKNON TÜREVLERİNİN ELEKTRONCA EKSİK ALKENLERLE REAKSİYONLARI

DOKTORA TEZİ
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ABANT İZZET BAYSAL ÜNİVERSİTESİ FEN BİLİMLERİ ENSTİTÜSÜ

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202 SAYFA
BOLU, MAYIS - 2015

Bu tez genel olarak, Münknon diye bilinen azometin ilidlerin özel bir türevi olan 1,3-oksazoliyum-5-oksidler ile elektronca eksik dipolarseven reaktif çeşitleriyle tepkimelerini kapsamaktadır. Bu bağlamda, pirolerin bir serisi, *N*-benzoil benamidler, *p*-substitue benzoik asitler ve *N*-açıl üreler elde edildi. Bu bileşikler, doğal ve birçok farmasetik bileşiklerde yaygın olarak bulunan önemli heterohalkalı yapılardır. Literatürde pirol türevlerini hazırlamak için bir çok sentetik yöntem vardır. Bunların arasında, yaygın olan yöntemlerden biri, münknonların alkin ve alkenler ile 1,3-dipolar halka katılma reaksiyonlarıdır. Bu tez çalışmasının asıl amacı, mezoionik münknonlar ile elektronca yoksun alkenlerin reaksiyonlarının incelenmesidir. Bu bileşiklerin sonuçları üç kısımda tartışılmıştır;

Birinci kısım tepkime ortamında *N*-açıl amino asitlerden üretilen münknonlar ile benzoitiyofen 1,1-dioksitin halka katılma reaksiyonu tanımlanmaktadır. Sulfon kısmının beraberindeki oksijen çıkışı benzoitiyofen birleşmiş pirol türevlerini meydana getirmiştir. Tüm reaksiyonu rasyonalize etmek için, beklenen ürün olan sulfidin sülfona dönüşümü *m*-kloroperbenzoik asit oksidasyonu ile gerçekleştirilmiştir.

Bu çalışmanın ikinci kısmı, tepkime ortamında 2-(4-sübstituefenil)-2-(*N*-metil-*N*-*p*-sübstituebenzamid)asetik asitlerden üretilen münknonların asetik anhidrit ile 2-nitrometilen tiyazolidin varlığında reaksiyonu ile elde edilen (*E*)-1-(*N*,4-dimetilbenzamid)-1-(4-florofenil)prop-1-in-2-il asetat, 4-aril-*N*-metil-*N*-(4-sübstituebenzoil)benzamidlerin ve *p*-sübstitue benzoik asitlerin sentezini içermektedir. Bu reaksiyonlar için Dakin-West tipi mekanizmalar önerilmiştir.

Bu tezin son bölümünde, bir baz ortamındaki Münknonlarla karbodiimidler arasındaki reaksiyonlar vasıtası ile *N*-açıl üre türevlerinin oluşumunu sağlayan etkin yeni bir yol tanımlanmıştır.

ANAHTAR KELİMELEER:

Münknon, 1,3-dipolar halka katılma, asetik anhidrit, Dakin-West, karbodimit, üre

TABLE OF CONTENTS

	<u>Page</u>
ABSTRACT	HATA! YER İŞARETİ TANIMLANMAMIŞ.
ÖZET.....	HATA! YER İŞARETİ TANIMLANMAMIŞ.
TABLE OF CONTENTS.....	VII
LIST OF SCHEMES	IX
LIST OF FIGURES	XII
LIST OF TABLES	XVII
LIST OF ABBREVIATIONS AND SYMBOLS	XVIII
ACKNOWLEDGEMENTS.....	XX
FORMULAE	XXI
1. INTRODUCTION.....	1
1.1 CHAPTER 1	1
1.1.1 1,3-Dipolar Cycloaddition	1
1.1.2 The 1,3-Dipoles and Dipolarophiles	1
1.1.3 Reaction Mechanism of 1,3-Dipolar Cycloaddition	3
1.2 CHAPTER 2	5
1.2.1 Introduction and Background of Münchnones and Synthesis of Pyrrole and Pyrrolidine.....	5
1.2.2 Münchnones.....	5
1.2.2.1 Synthesis of Münchnones.....	5
1.2.2.1.1 By Cyclodehydration of Amino Acids	6
1.2.2.1.2 By Isomerization of Oxazolones.....	7
1.2.2.1.3 By Metal-Mediated Routes.....	9
1.2.2.1.4 By Ugi Reactions	10
1.2.2.1.5 Other Methods for Preparation of Münchnones	10
1.2.2.1.5.1 1,3-Thiazolium-5-Thiolates	10
1.2.2.1.5.2 Phospha-Münchnones	11
1.2.2.2 1,3-Dipolar Cycloaddition Reactions of Münchnones and Synthesis of Pyrrole and Pyrrolidine	11
1.2.2.2.1 Synthesis of Pyrrole Derivatives.....	12
1.2.2.2.2 Synthesis of Pyrroline Derivatives	17
1.2.2.2.3 Reactions of Hetero-Dipolarophiles with Münchnones.....	19
1.2.2.2.4 Recent Applications for 1,3-Dipolar Cycloaddition Reactions of Münchnones	22
1.2.2.2.5 Biological Importance of Pyrrole Derivatives	23
1.3 CHAPTER 3	26

1.3.1 Dakin West Reaction	26
1.4 CHAPTER 4	31
1.4.1 N-Acylurea.....	31
1.5 CHAPTER 5	35
1.5.1 Benzo[b]thiophene 1,1-dioxide, 2-nitromethylene thiazolidine and sulfone.....	35
1.5.1.1 Benzo[b]thiophene 1,1-dioxide	35
1.5.1.2 2-Nitromethylene thiazolidine.....	36
2. AIM AND SCOPE OF THE STUDY	39
3. MATERIALS AND METHODS	40
4. RESULTS AND DISCUSSIONS	66
5. CONCLUSION.....	96
6. REFERENCES.....	97
7. APPENDICES	109
8. CURRICULUM VITAE	201

LIST OF SCHEMES

	<u>Page</u>
Scheme 1.1.1 Cyloaddition reactions mechanism.....	1
Scheme 1.1.2 Mechanism of 1,3-dipolar cycloaddition in concerted manner	3
Scheme 1.1.3 1,3-Dipolar cycloaddition in diradicalic manner.....	4
Scheme 1.2.1 General strategy for münchnone synthesis.....	6
Scheme 1.2.2 Cyclodehydration strategy to form münchnones.....	7
Scheme 1.2.3 Synthesis of 1,3-oxazolonium perchlorates.....	7
Scheme 1.2.4 Synthesis of Münchnones from oxazolones.....	8
Scheme 1.2.5 Generation of Münchnones from 5-siloxyoxazoles	8
Scheme 1.2.6 Preparation of Münchnones from in situ alkylation of azlactones	9
Scheme 1.2.7 Metal-Catalyzed münchnone synthesis	9
Scheme 1.2.8 Organometallic complexes precursors for münchnone generation	9
Scheme 1.2.9 Münchnone generation via Ugi adducts	10
Scheme 1.2.10 Synthesis of 1,3-thiazolium-5-thiolates.....	10
Scheme 1.2.11 Generation of phospho-Münchnones.....	11
Scheme 1.2.12 Common cycloaddition products of Münchnones.....	12
Scheme 1.2.13 1,3-dipolar cycloaddition of Münchnone with methyl propiolate.....	12
Scheme 1.2.14 Cycloaddition of Münchnone with DMAD.....	13
Scheme 1.2.15 Synthesis of some pyrrole derivatives using variety of Münchnones .	14
Scheme 1.2.16 Substituent effects on Münchnone formation and reactivity.....	15
Scheme 1.2.17 Alkene cycloaddition in pyrrole synthesis	16
Scheme 1.2.18 Münchnone-Alkene cycloaddition followed by oxidation to pyrrole	16
Scheme 1.2.19 Cycloaddition of Münchnones and unusual dipolarophile.....	17
Scheme 1.2.20 Synthesis of pyrrolines via intramolecular alkene cycloaddition.....	18
Scheme 1.2.21 Lewis acid and gold catalyzed-mediated synthesis of pyrrolines	19
Scheme 1.2.22 Synthesis of pyrroline with azlactone and fullerene.....	19
Scheme 1.2.23 Cycloaddition reaction of Münchnone with phosphaaalkyne	20
Scheme 1.2.24 Synthesis of imidazoles via phospho-Münchnone cycloaddition with nitrile.....	20
Scheme 1.2.25 Preparation of the 1,2,4-triazoles via 1,3-oxazolium-5-olates (Münchnones)	20
Scheme 1.2.26 Synthesis of imidazole from Münchnone/imine cycloaddition.....	21
Scheme 1.2.27 Cycloaddition reactions of palladium-catalyzed Münchnones with imines.....	21
Scheme 1.2.28 Reaction of arynes with Münchnones	22
Scheme 1.2.29 Synthesis of (-)-Rhazinilam.....	23
Scheme 1.3.1 Synthesis of α -acetamido methyl ketone.....	26
Scheme 1.3.2 Mechanism of Dakin-West type reactions	27
Scheme 1.3.3 Preparation of ketomethylene peptide analogues	27
Scheme 1.3.4 Synthesis of acetamide.....	28

Scheme 1.3.5 Solid catalyst Dakin-West reaction of acetamido ketones	28
Scheme 1.3.6 Metal catalyst modified Dakin-West condensation	29
Scheme 1.3.7 Synthesis of perfluoro ketone	29
Scheme 1.3.8 Synthesis of compound 151	30
Scheme 1.3.9 Dakin-West reaction of carboxylic acid	30
Scheme 1.3.10 The Dakin-West reaction of N-acylprolines with inorganic base	30
Scheme 1.4.1 Reaction of acetic acid with carbodiimide	31
Scheme 1.4.2 Formation of compound 164	32
Scheme 1.4.3 Synthesis of N-acylurea derivatives in the presence of buffer solution	32
Scheme 1.4.4 The methods for the preparation of N-acylureas	33
Scheme 1.4.5 MW-assisted synthesis of N-acylurea derivatives	33
Scheme 1.4.6 N-heterocyclic carbene catalyzed formation of N-acylureas	34
Scheme 1.5.1 1,3-dipolar cycloaddition reactions of benzo[b]thiophene 1,1-dioxide	35
Scheme 1.5.2 Synthesis of 2-nitromethylene thiazolidine	36
Scheme 1.5.3 Multicomponent reaction	36
Scheme 1.5.4 Multicomponent cyclisation and one-pot cyclocondensation reactions of 2-nitromethylene thiazolidine	37
Scheme 1.5.5 Microwave-assisted coupling reaction of N-aryl sydnone with 2-nitromethylenethiazolidine	37
Scheme 1.5.6 Cycloaddition reaction of sulfolene	38
Scheme 1.5.7 Diels-Alder reaction of sulfolenes	38
Scheme 4.1 Synthesis of fused pyrrole derivatives	67
Scheme 4.2 Synthesis of N-acyl amino acids	68
Scheme 4.3 Cycloadditions of Münchnones 206 to benzo[b]thiophene 1,1-dioxide 177 affording 207 ^{a,b}	71
Scheme 4.4 Cycloadditions of Münchnone 206d to benzo[b]thiophene 1,1-dioxide 177 affording regioisomers 207d and 207d'	72
Scheme 4.5 Münchnone 206 and benzo[b]thiophene 220 did not undergo reaction under the different conditions	73
Scheme 4.6 Different strategies for the synthesis of fused pyrrole derivatives	74
Scheme 4.7 m-CPBA oxidation of cycloadduct 207e	75
Scheme 4.8 Possible products of münchnone 221-2-nitromethylenethiazolidine 184 1,3-dipolar cycloaddition leading to spiro or fused heterocycles.	78
Scheme 4.9 Reactions between 206b and acetic anhydride in the presence of 2-nitromethylenethiazolidine 184 and pyridine to afford enol ester 209	79
Scheme 4.10 Formation of enol ester with using different strategies	80
Scheme 4.11 Plausible mechanism for the synthesis enol ester 209	82
Scheme 4.12 Possible reaction mechanism involving carbon monoxide release leading to substituted benzamides 210	85
Scheme 4.13 Structure of ionic fragment at m/z 297 of 210d	86
Scheme 4.14 Possible reaction mechanism leading to 4-substituted benzoic acids 211	87

Scheme 4.15 N-Acetyl-N-methyl substituted amino acid 206k did not undergo reaction under the specified conditions	90
Scheme 4.16 Possible products of Münchnone-3-(phenylsulfonyl)-2,5- dihydrothiophene 1,1-dioxide 194 1,3-dipolar cycloaddition leading to fused heterocycles.	91
Scheme 4.17 Synthesis of N-acylurea derivatives 213 and 214	94
Scheme 4.118 Plausible reaction mechanism of N-acylurea derivatives 213 and 214	95



LIST OF FIGURES

Figure 1.1.1 Allyl and propargyl/allenyl type dipoles	2
Figure 1.1.2 Examples of some dipolarophiles.....	3
Figure 1.1.3 Molecular orbital control of 1,3-dipolar cycloaddition	4
Figure 1.2.1 Resonance structures of Münchnones	5
Figure 1.2.2 Some of the non-naturally biologically important pyrroles.....	24
Figure 1.2.3 Structure of polycitone A and storniamides A-D	25
Figure 1.4.1 Structure of Cabergoline, inhibitors of fall armyworm and house fly...	31
Figure 4.1 X-Ray ORTEP view of 207c	69
Figure 4.2 Comparing ¹ H NMR of sulfide and sulfone cycloadduct 207e and 208e.	76
Figure 4.3 X-Ray diffraction for compound 208e	77
Figure 4.4 X-Ray ORTEP view of enol ester 209	80
Figure 4.5 ¹ H NMR Spectrum of compounds 209 and 210d	83
Figure 4.6 X-Ray ORTEP view of 210d.....	84
Figure 4.7 An ORTEP projection of compound 211f.....	88
Figure 4.8 ¹ H NMR spectrum of compounds 213d and 214d.....	92
Figure 4.9 An ORTEP projection of compound 214e.....	93
Figure A.1 IR Spectrum of compound 204a	109
Figure A.2 ¹ H NMR Spectrum of compound 204a.....	109
Figure A.3 IR Spectrum of compound 204b.....	110
Figure A.4 ¹ H NMR Spectrum of compound 204b	110
Figure A.5 ¹³ C NMR Spectrum of compound 204b	111
Figure A.6 IR Spectrum of compound 206a	111
Figure A.7 ¹ H NMR Spectrum of compound 206a.....	112
Figure A.8 ¹³ C NMR Spectrum of compound 206	112
Figure A.9 IR Spectrum of compound 206b.....	113
Figure A.10 ¹ H NMR Spectrum of compound 206b.....	113
Figure A.11 ¹³ C NMR Spectrum of compound 206b	114
Figure A.12 IR Spectra of compound 206c	114
Figure A.13 ¹ H NMR Spectrum of compound 206c.....	115
Figure A.14 ¹³ C NMR Spectrum of compound 206c.....	115
Figure A.15 IR Spectrum of compound 206d.....	116
Figure A.16 ¹ H NMR Spectrum of compound 206d.....	116
Figure A.17 ¹³ C NMR Spectrum of compound 206d	117
Figure A.18 IR Spectrum of compound 206e	117
Figure A.19 ¹ H NMR Spectrum of compound 206e.....	118
Figure A.20 ¹³ C NMR Spectrum of compound 206e.....	118
Figure A.21 IR Spectrum of compound 206f	119
Figure A.22 ¹ H NMR Spectrum of compound 206f	119
Figure A.23 ¹³ C NMR Spectrum of compound 206f	120
Figure A.24 IR Spectrum of compound 206g.....	120
Figure A.25 ¹ H NMR Spectrum of compound 206g.....	121

Figure A.26 ^{13}C NMR Spectrum of compound 206g	121
Figure A.27 IR Spectrum of compound 206h.....	122
Figure A.28 ^1H NMR Spectrum of compound 206h.....	122
Figure A.29 ^{13}C NMR Spectrum of compound 206h	123
Figure A.30 IR Spectrum of compound 206i.....	123
Figure A.31 ^1H NMR Spectrum of compound 206i	124
Figure A.32 ^{13}C NMR Spectrum of compound 206i	124
Figure A.33 IR Spectrum of compound 206j.....	125
Figure A.34 ^1H NMR Spectrum of compound 206j	125
Figure A.35 ^{13}C NMR Spectrum of compound 206j	126
Figure A.36 IR Spectrum of compound 206k.....	126
Figure A.37 ^1H NMR Spectrum of compound 206k.....	127
Figure A.38 ^{13}C NMR Spectrum of compound 206k	127
Figure A.39 ^1H NMR Spectrum of compound 206l	128
Figure A.40 ^1H NMR Spectrum of compound 207a.....	128
Figure A.41 ^{13}C NMR Spectrum of compound 207a.....	129
Figure A.42 MASS Spectrum of compound 207a	129
Figure A.43 IR Spectra of compound 207b	130
Figure A.44 ^1H NMR Spectrum of compound 207b.....	130
Figure A.45 ^{13}C NMR Spectrum of compound 207b	131
Figure A.46 IR Spectrum of compound 207c	131
Figure A.47 ^1H NMR Spectrum of compound 207c.....	132
Figure A.48 ^{13}C NMR Spectrum of compound 207c.....	132
Figure A.49 MASS Spectrum of compound 207c	133
Figure A.50 IR Spectrum of compound 207d.....	133
Figure A.51 ^1H NMR Spectrum of compound 207d	134
Figure A.52 ^{13}C NMR Spectrum of compound 207d	134
Figure A.53 IR Spectrum of compound 207e	135
Figure A.54 ^1H NMR Spectrum of compound 207e.....	135
Figure A.55 ^{13}C NMR Spectrum of compound 207e.....	136
Figure A.56 MASS Spectrum of compound 207e	136
Figure A.57 IR Spectrum of compound 207f	137
Figure A.58 ^1H NMR Spectrum of compound 207f	137
Figure A.59 ^{13}C NMR Spectrum of compound 207f.....	138
Figure A.60 MASS Spectrum of compound 207f.....	138
Figure A.61 IR Spectrum of compound 207g.....	139
Figure A.62 ^1H NMR Spectrum of compound 207g.....	139
Figure A.63 ^{13}C NMR Spectrum of compound 207g	140
Figure A.64 IR Spectrum of compound 207h.....	140
Figure A.65 ^1H NMR Spectrum of compound 207h.....	141
Figure A.66 ^{13}C NMR Spectrum of compound 207h	141
Figure A.67 IR Spectrum of compound 207i.....	142
Figure A.68 ^1H NMR Spectrum of compound 207i	142
Figure A.69 ^{13}C NMR Spectrum of compound 207i	143

Figure A.70 IR Spectrum of compound 207j.....	143
Figure A.71 ^1H NMR Spectrum of compound 207j	144
Figure A.72 ^{13}C NMR Spectrum of compound 207j	144
Figure A.73 MASS Spectrum of compound 207j.....	145
Figure A.74 IR Spectrum of compound 207k.....	145
Figure A.75 ^1H NMR Spectrum of compound 207k.....	146
Figure A.76 ^{13}C NMR Spectrum of compound 207k	146
Figure A.77 IR Spectrum of compound 208e	147
Figure A.78 ^1H NMR Spectrum of compound 208e.....	147
Figure A.79 ^{13}C NMR Spectrum of compound 208e.....	148
Figure A.80 MASS Spectrum of compound 208e	148
Figure A.81 IR Spectrum of compound 209.....	149
Figure A.82 ^1H NMR Spectrum of compound 209.....	149
Figure A.83 ^{13}C NMR Spectrum of compound 209	150
Figure A.84 MASS Spectrum of compound 209	150
Figure A.85 IR Spectrum of compound 210d.....	151
Figure A.86 ^1H NMR Spectrum of compound 210d.....	151
Figure A.87 ^{13}C NMR Spectrum of compound 210d	152
Figure A.88 MASS Spectrum of compound 210d	152
Figure A.89 IR Spectrum of compound 210f	153
Figure A.90 ^1H NMR Spectrum of compound 210f	153
Figure A.91 ^{13}C NMR Spectrum of compound 210f	154
Figure A.92 MASS Spectrum of compound 210f.....	154
Figure A.93 IR Spectrum of compound 210h.....	155
Figure A.94 ^1H NMR Spectrum of compound 210h.....	155
Figure A.95 ^{13}C NMR Spectrum of compound 210h	156
Figure A.96 MASS Spectrum of compound 210h	156
Figure A.97 IR Spectrum of compound 210i.....	157
Figure A.98 ^1H NMR Spectrum of compound 210i	157
Figure A.99 ^{13}C NMR Spectrum of compound 210i	158
Figure A.100 MASS Spectrum of compound 210i.....	158
Figure A.101 IR Spectrum of compound 210j.....	159
Figure A.102 ^1H NMR Spectrum of compound 210j	159
Figure A.103 ^{13}C NMR Spectrum of compound 210j	160
Figure A.104 MASS Spectrum of compound 210j.....	160
Figure A.105 IR Spectrum of compound 211a	161
Figure A.106 ^1H NMR Spectrum of compound 211a.....	161
Figure A.107 ^{13}C NMR Spectrum of compound 211a.....	162
Figure A.108 MASS Spectrum of compound 211a	162
Figure A.109 IR Spectrum of compound 211b.....	163
Figure A.110 ^1H NMR Spectrum of compound 211b.....	163
Figure A.111 ^{13}C NMR Spectrum of compound 211b	164
Figure A.112 MASS Spectrum of compound 211b	164
Figure A.113 IR Spectrum of compound 211c	165

Figure A.114 ^1H NMR Spectrum of compound 211c.....	165
Figure A.115 ^{13}C NMR Spectrum of compound 211c.....	166
Figure A.116 MASS Spectrum of compound 211c	166
Figure A.117 IR Spectrum of compound 211d.....	167
Figure A.118 ^1H NMR Spectrum of compound 211d.....	167
Figure A.119 ^{13}C NMR Spectrum of compound 211d	168
Figure A.120 MASS Spectrum of compound 211d.....	168
Figure A.121 IR Spectrum of compound 211e	169
Figure A.122 ^1H NMR Spectrum of compound 211e.....	169
Figure A.123 ^{13}C NMR Spectrum of compound 211e.....	170
Figure A.124 MASS Spectrum of compound 211e	170
Figure A.125 IR Spectrum of compound 211f	171
Figure A.126 ^1H NMR Spectrum of compound 211f	171
Figure A.127 ^{13}C NMR Spectrum of compound 211f.....	172
Figure A.128 MASS Spectrum of compound 211f.....	172
Figure A.129 IR Spectrum of compound 211g.....	173
Figure A.130 ^1H NMR Spectrum of compound 211g.....	173
Figure A.131 ^{13}C NMR Spectrum of compound 211g	174
Figure A.132 MASS Spectrum of compound 211g.....	174
Figure A.133 IR Spectrum of compound 213a	175
Figure A.134 ^1H NMR Spectrum of compound 213a.....	175
Figure A.135 ^{13}C NMR Spectrum of compound 213a.....	176
Figure A.136 MASS Spectrum of compound 213a	176
Figure A.137 IR Spectrum of compound 213b.....	177
Figure A.138 ^1H NMR Spectrum of compound 213b.....	177
Figure A.139 ^{13}C NMR Spectrum of compound 213b	178
Figure A.140 MASS Spectrum of compound 213b	178
Figure A.141 IR Spectrum of compound 213c	179
Figure A.142 ^1H NMR Spectrum of compound 213c.....	179
Figure A.143 ^{13}C NMR Spectrum of compound 213c.....	180
Figure A.144 MASS Spectrum of compound 213c	180
Figure A.145 IR Spectrum of compound 213d.....	181
Figure A.146 ^1H NMR Spectrum of compound 213d.....	181
Figure A.147 ^{13}C NMR Spectrum of compound 213d	182
Figure A.148 MASS Spectrum of compound 213d.....	182
Figure A.149 IR Spectrum of compound 213e	183
Figure A.150 ^1H NMR Spectrum of compound 213e.....	183
Figure A.151 ^{13}C NMR Spectrum of compound 213e.....	184
Figure A.152 MASS Spectrum of compound 213e	184
Figure A.153 ^1H NMR Spectrum of compound 213f	185
Figure A.154 ^{13}C NMR Spectrum of compound 213f.....	185
Figure A.155 MASS Spectrum of compound 213f.....	186
Figure A.156 IR Spectrum of compound 214a	186
Figure A.157 ^1H NMR Spectrum of compound 214a.....	187

Figure A.158 ^{13}C NMR Spectrum of compound 214a.....	187
Figure A.159 MASS Spectrum of compound 214a	188
Figure A.160 IR Spectrum of compound 214b.....	188
Figure A.161 ^1H NMR Spectrum of compound 214b.....	189
Figure A.162 ^{13}C NMR Spectrum of compound 214b	189
Figure A.163 MASS Spectrum of compound 214b	190
Figure A.164 IR Spectrum of compound 214c	190
Figure A.165 ^1H NMR Spectrum of compound 214c.....	191
Figure A.166 ^{13}C NMR Spectrum of compound 214c.....	191
Figure A.167 MASS Spectrum of compound 214c	192
Figure A.168 IR Spectrum of compound 214d.....	192
Figure A.169 ^1H NMR Spectrum of compound 214d.....	193
Figure A.170 ^{13}C NMR Spectrum of compound 214d	193
Figure A.171 MASS Spectrum of compound 214d.....	194
Figure A.172 IR Spectrum of compound 214e	194
Figure A.173 ^1H NMR Spectrum of compound 214e.....	195
Figure A.174 ^{13}C NMR Spectrum of compound 214e.....	195
Figure A.175 MASS Spectrum of compound 214e	196
Figure A.176 IR Spectrum of compound 214f	196
Figure A.177 ^1H NMR Spectrum of compound 214f	197
Figure A.178 ^{13}C NMR Spectrum of compound 214f.....	197
Figure A.179 MASS Spectrum of compound 214f.....	198
Figure A.180 IR Spectrum of compound 214g.....	198
Figure A.181 ^1H NMR Spectrum of compound 214g.....	199
Figure A.182 ^{13}C NMR Spectrum of compound 214g	199
Figure A.183 MASS Spectrum of compound 214g.....	200

LIST OF TABLES

Table 4.1 Optimization of reaction conditions to yield compound 207a.....	73
Table 4.2 Products obtained from the reaction between Münchnone precursors 206 and acetic anhydride in the presence of 2-nitromethylenethiazolidine 184 with yields.....	89



LIST OF ABBREVIATIONS AND SYMBOLS

1,3-DC	: 1,3- Dipolar Cycloaddition
Ac₂O	: Acetic Anhydride
CDCl₃	: Deuterated Chloroform
CFAA	: Chlorodifluoroacetic Anhydride
CHCl₃	: Chloroform
CO	: Carbon Monoxide
CO₂	: Carbon Dioxide
d	: Doublet (NMR)
DCC	: <i>N,N'</i> -Dicyclohexylcarbodiimide
dd	: Doublet of Doublets (NMR)
ddd	: Doublet of Doublet of Doublets (NMR)
DIPA	: Diisopropyl Amine
DIPC	: <i>N,N'</i> -Diisopropylcarbodiimide
DMAD	: Dimethylacetylenedicarboxylate
DMSO	: Dimethylsulfoxide
EDC	: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ES⁻	: Electrospray Ionization (Negative)
ES⁺	: Electrospray Ionization (Positive)
FMO	: Frontier Molecular Orbital
HCl	: Hydrochloric Acid
HOMO	: Highest Occupied Molecular Orbital
HRMS	: High Resolution Mass Spectrometry
Hz	: Hertz
IR	: Infrared Spectroscopy
J	: Coupling Constants (NMR)
LUMO	: Lowest Occupied Molecular Orbital
m	: Multiplet (NMR)
M.p.	: Melting Point
<i>m</i>-CPBA	: <i>m</i> -Chloroperbenzoic
MS	: Mass Spectrometry
MW	: Microwave Radiation
PPM	: Parts Per Million (NMR)

q	: Quartet (NMR)
s	: Singlet (NMR)
t	:Triplet (NMR)
TFAA	: Trifluoroacetic Anhydride
TMS	: Tetramethylsilane
TOF	: Time of Flight
δ	: Chemical Shift (NMR)



ACKNOWLEDGEMENTS

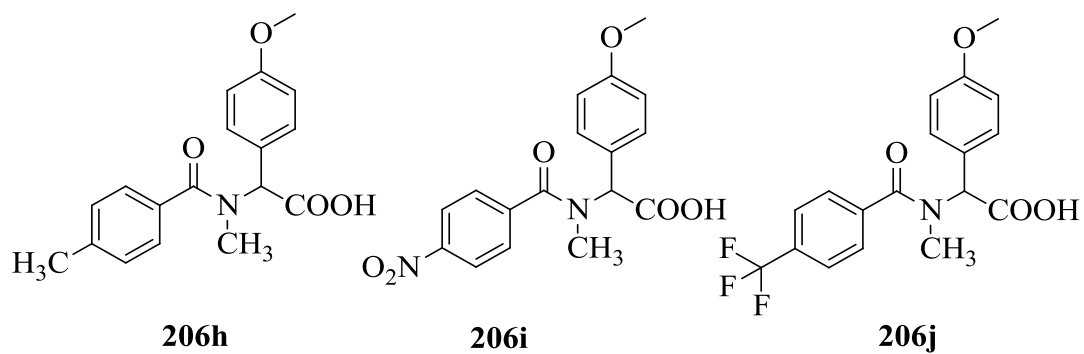
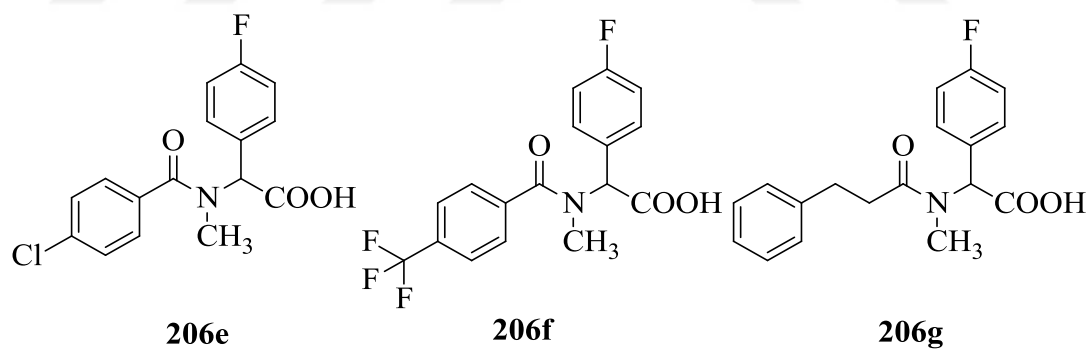
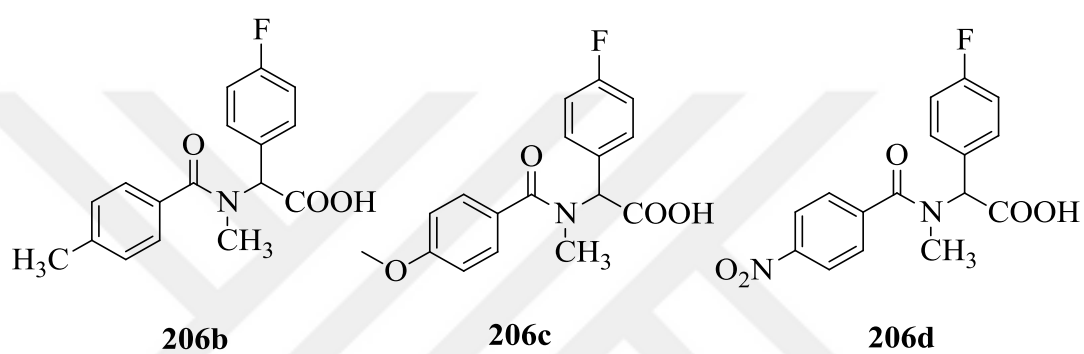
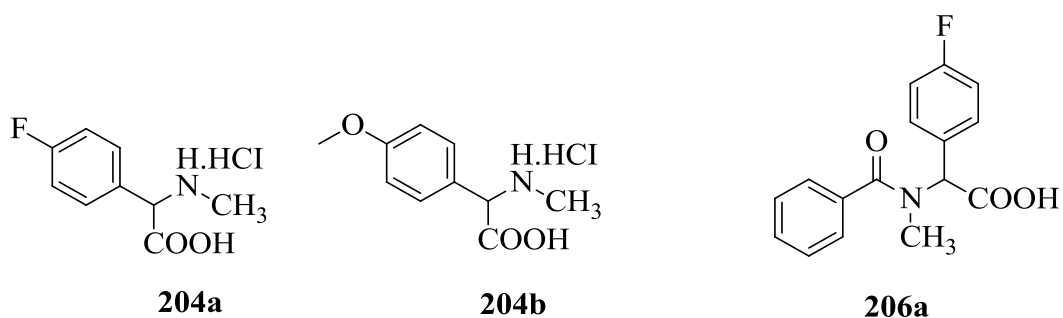
First and foremost, I would like to thank my research advisor, Professor Yaşar Dürüst for his help, advice, encouragement, trust and continued guidance at all time.

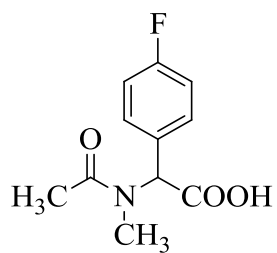
I would also like to sincerely thank to all my previous and current colleagues at Prof. Dürüst's lab for all the help and fun they provided. Specifically, I would like to thank Assist. Prof. Dr. Muhammet Yıldırım, Associate Prof. Dr. Cevher Altuğ, Assist. Prof. Dr. Erol Akpınar, Muhammed Tural Ateş, Eda Sağırlı and Akın Sağırlı.

Finally, I would like to thank my parents, for their unconditional love and support throughout my entire education. Everything I have accomplished has been derived from the values they taught me.

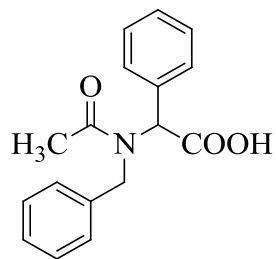
I would like to thank Scientific and Technological Research Council of Turkey (Project No-211T037) for the financial support for my study.

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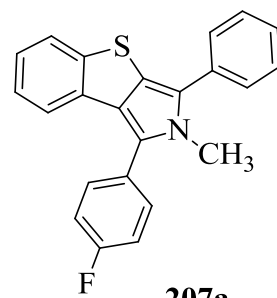




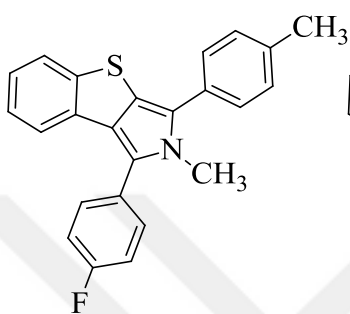
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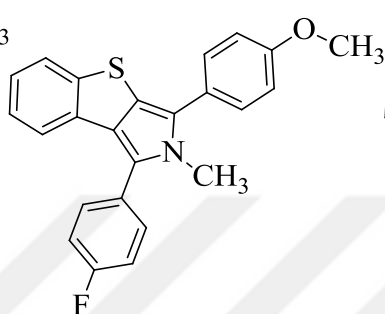
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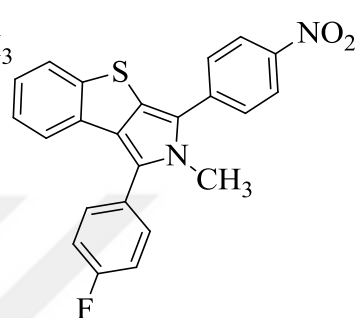
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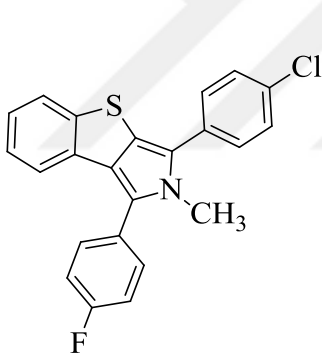
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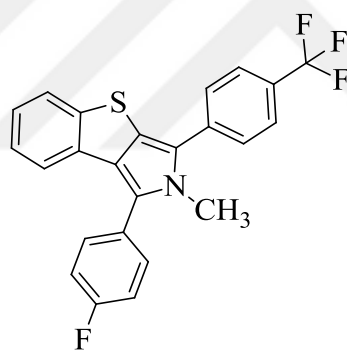
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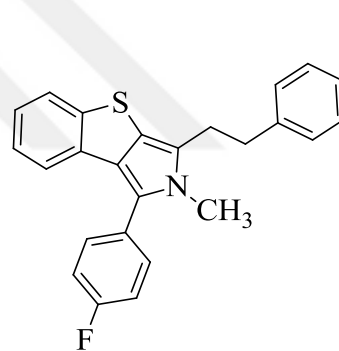
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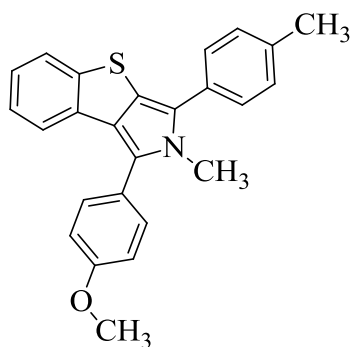
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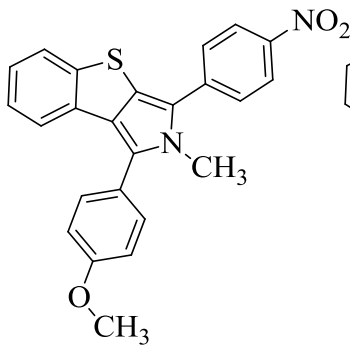
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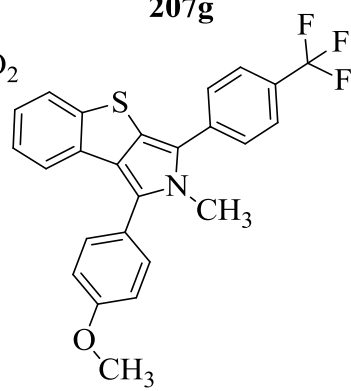
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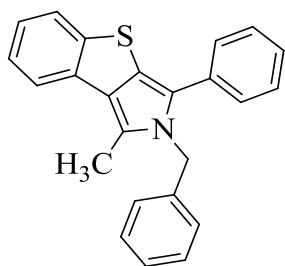
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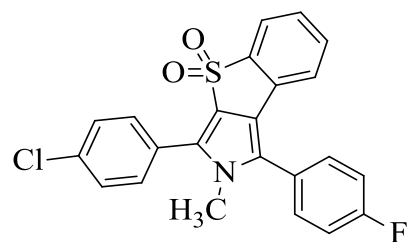
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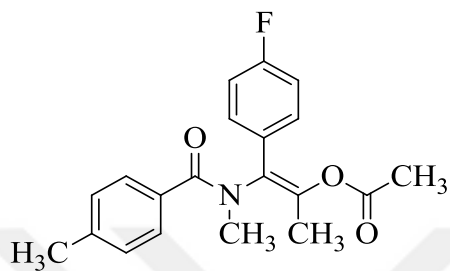
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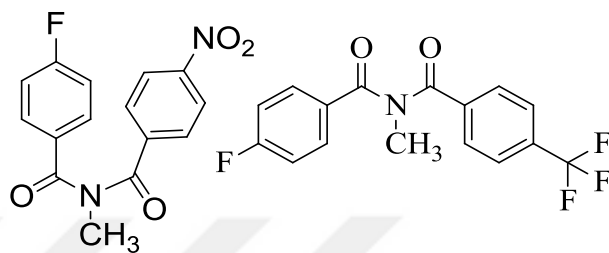
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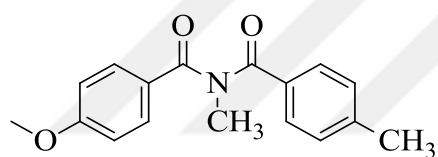


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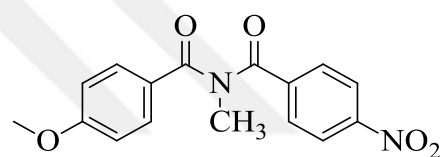


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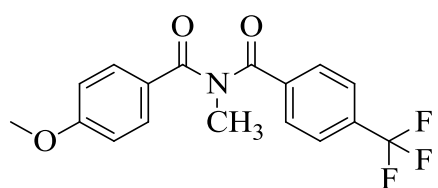
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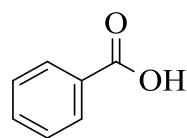
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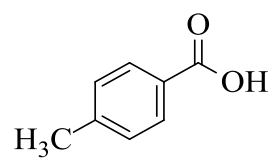
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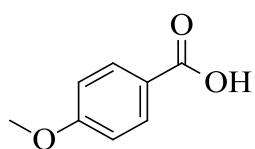
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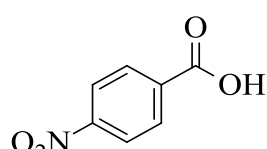
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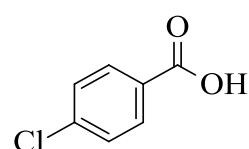
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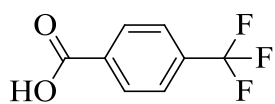
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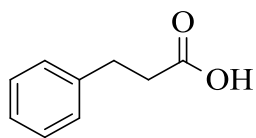
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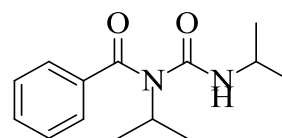
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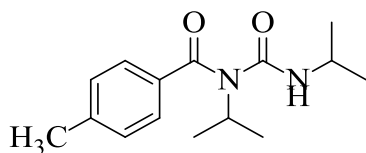
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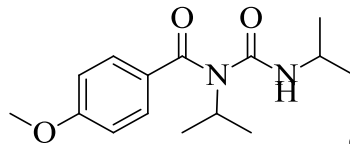
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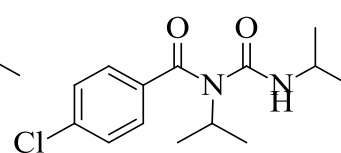
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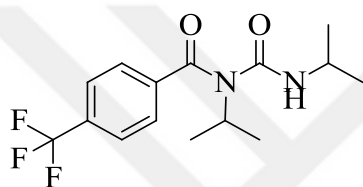
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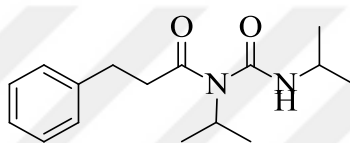
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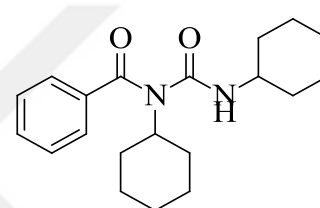
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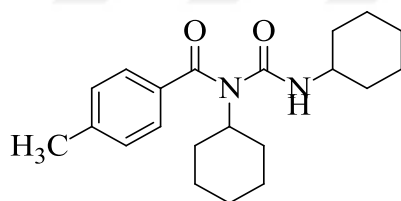
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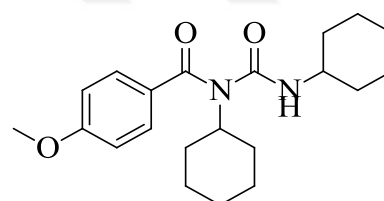
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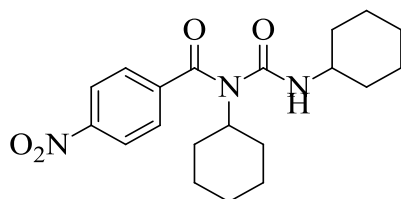
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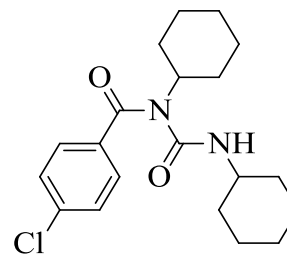
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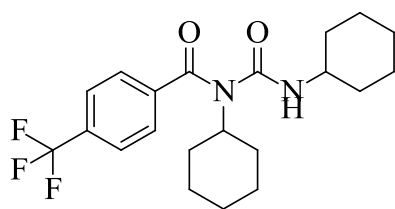
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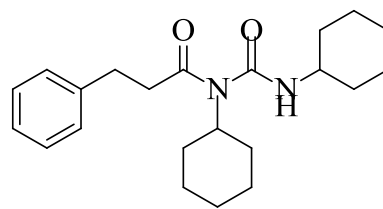
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214e



214f



214g



1. INTRODUCTION

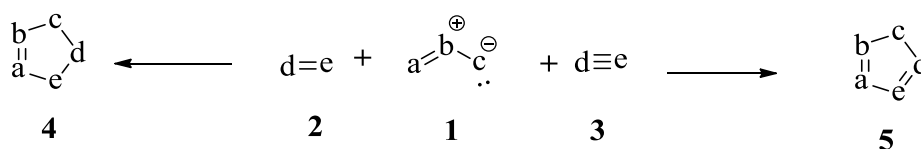
1.1 CHAPTER 1

1.1.1 1,3-Dipolar Cycloaddition

1,3-dipolar cycloaddition (DC) reactions are one of the most important class of reactions with both mechanistic and synthetic interest in organic chemistry. The mechanistic investigation and synthetic application of 1,3-dipolar cycloaddition were established by Huisgen and his co-workers in 1960s (Huisgen, 1961). The 1,3-dipolar cycloaddition reaction is a reaction between a 1,3-dipole and a dipolarophile, combine to form a five-membered heterocycles (Huisgen, 1963).

1.1.2 The 1,3-Dipoles and Dipolarophiles

A 1,3-dipole is an organic molecule that is a reactive compound with a distributed charge, which forms a five-membered ring with a dipolarophile may contain any double or triple bond (Scheme 1. 1).

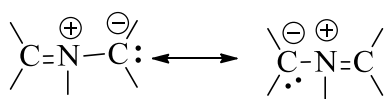


Scheme 1.1.1 Cycloaddition reactions mechanism

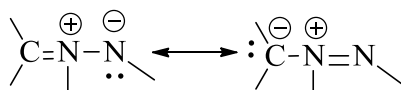
1,3-dipole can be divided into two groups by the incorporation of an additional π bond. The propargyl/allenyl anion type which has a linear structure and the allyl anion type with a bent structure (Figure 1.1.1) (Huisgen, 1963).

Allyl Type

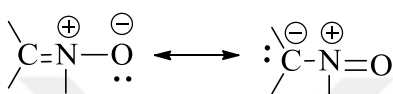
Azomethine Ylides



Azomethine Imines



Nitrone



Carbonyl Ylides

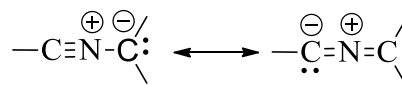


Ozone

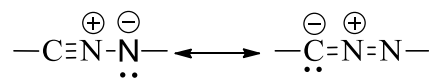


Propargyl/Allenyl Type

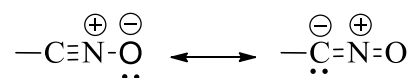
Nitrile Ylides



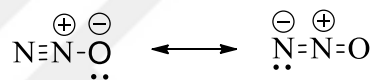
Nitrile Imines



Nitrile Oxides



Nitrous Oxide



Azide



Figure 1.1.1 Allyl and Propargyl/Allenyl type dipoles

Mesoionic compounds react as dipoles in 1,3-dipolar cycloadditions that are relatively stable cyclic compounds. Azomethine ylide-type münchnones and azlactones and azomethine imine-type sydnones are the most common mesoionic compounds.

The dipolarophile is a 2 π electron species that reacts with 1,3-dipoles in 1,3-dipolar cycloaddition reactions. Electron deficient dipolarophiles are generally used for a model as dipolarophiles in 1,3-DC reactions. α , β -unsaturated aldehydes, ketones, allylic alcohols, allylic halides, imines, vinylic ethers and alkynes are examples of dipolarophiles (Figure 1.1.2) (Houk, 1973).

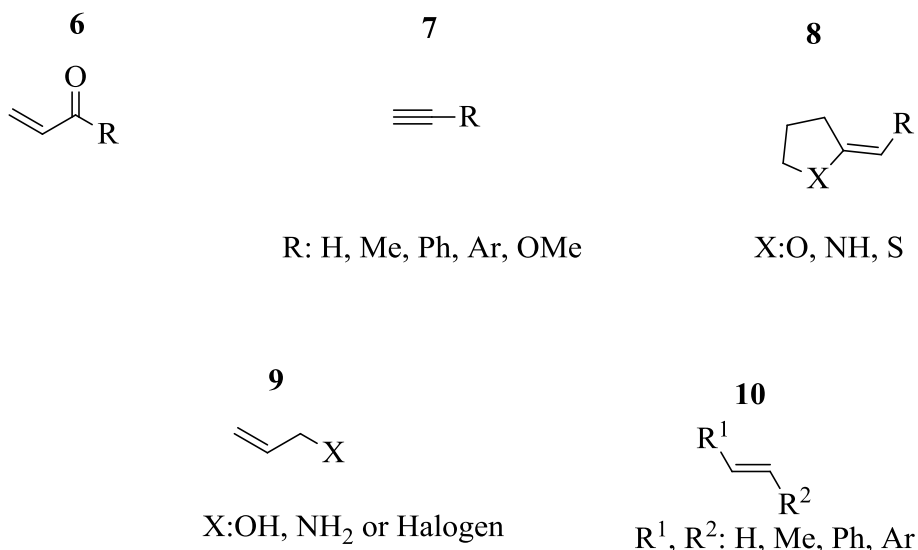
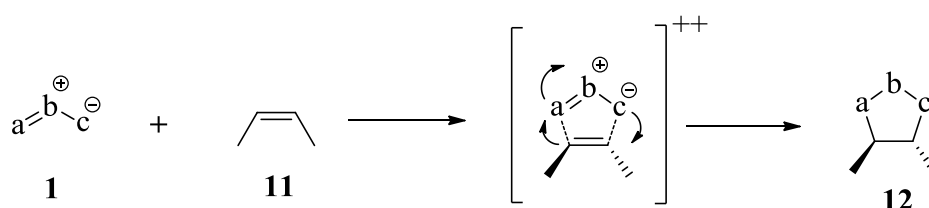


Figure 1.1.2 Examples of some dipolarophiles

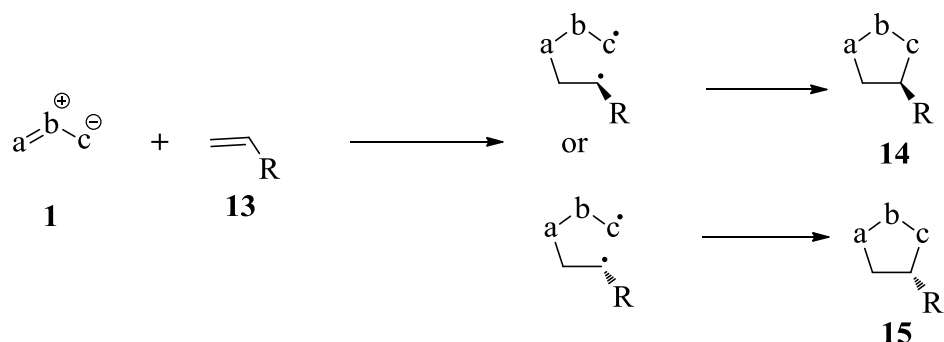
1.1.3 Reaction Mechanism of 1,3-Dipolar Cycloaddition

The mechanism of 1,3-dipolar cycloaddition has been intensively investigated. In the 1960s, Huisgen published the first mechanistic study (Huisgen, 1963). The accepted mechanism of most 1,3-dipolar cycloadditions proceed through single concerted step (Scheme 1.1.2), where the two new σ -bonds are usually formed to different extents in the transition state.



Scheme 1.1.2 Mechanism of 1,3-dipolar cycloaddition in concerted manner

Firestone et al. (1967) claimed that, 1,3-dipolar cycloaddition reactions proceed through a singlet diradical intermediate which the mechanism involves two stages but this mechanism is now deprecated (Firestone, 1967 and 1972).



Scheme 1.1.3 1,3-Dipolar cycloaddition in diradicalic manner

Woodward and Hoffman (1969) which developed the interacting π electron model defined the concepts of pericyclic reactions and orbital symmetry.

The reactivity of 1,3-dipoles and dipolarophiles vary considerably and the variation has been explained with a Frontier Molecular Orbital (FMO) theory. 1,3-Dipolar cycloadditions are highest occupied molecular orbital (HOMO)–lowest occupied molecular orbital (LUMO) controlled reactions. There are three limiting cases, where the transition state may be approximated by only the $\text{HOMO}_{\text{dipolarophile}} - \text{LUMO}_{\text{dipole}}$, both HOMO-LUMO combinations, or $\text{HOMO}_{\text{dipole}} - \text{LUMO}_{\text{dipolarophile}}$ interactions. The overlap of the LUMO and HOMO orbitals is maximized during the cycloaddition (Houk, 1973).

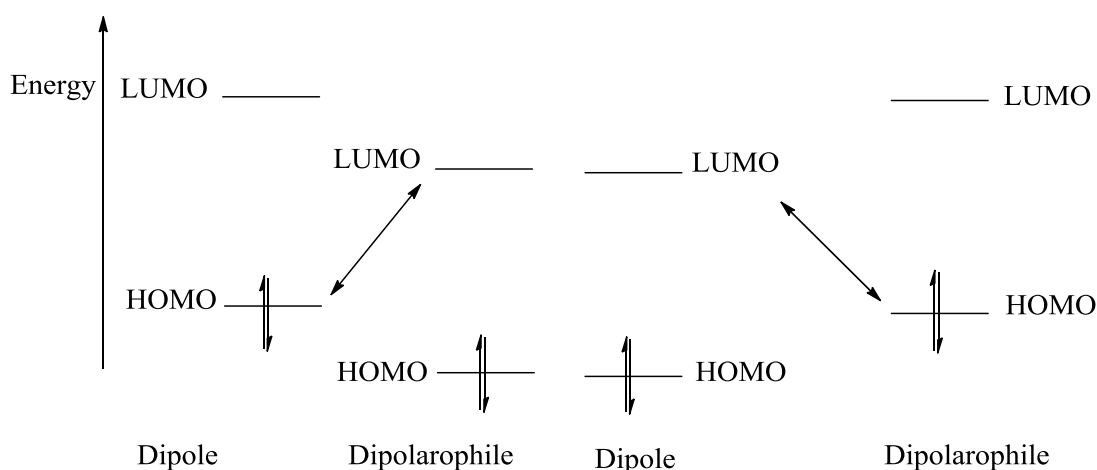


Figure 1.1.3 Molecular orbital control of 1,3-dipolar cycloaddition

1.2 CHAPTER 2

1.2.1 Introduction and Background of Münchnones and Synthesis of Pyrrole and Pyrrolidine

1.2.2 Münchnones

Münchnones, so called, 1,3-oxazolium-5-olates, are among the five-membered mesoionic compounds which were firstly obtained and investigated at the University of Munich. Preparation of a münchnone derivative was reported firstly by Lawson & Miles in 1958 by cyclodehydration of 2-pyridone-*N*-acetic acid with acetic anhydride (Lawson, 1958).

Mesoionic compounds are relatively stable cyclic compounds have been known for many years and have been extensively utilized as substrates in 1,3-dipolar cycloaddition reactions. Among the most common mesoionic compounds are azomethine ylide-type münchnones and azlactones and azomethine imine-type sydnones. Of the known mesoionic heterocycles, münchnones have generated considerable interest in recent decades. The 1,3-dipolar cycloaddition of münchnones was first reported by Huisgen and co-workers (Padwa, 1984; Huisgen, 1964; Gotthardt, 1964, 1970).

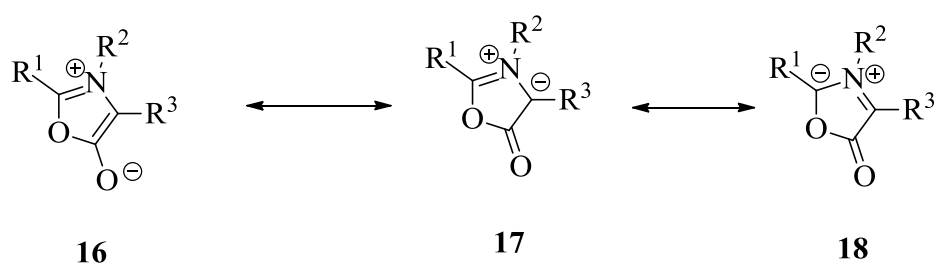
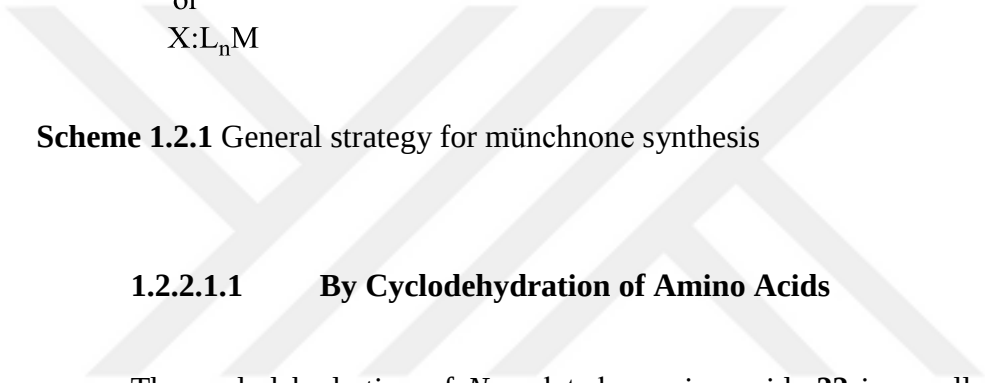


Figure 1.2.1 Resonance structures of Münchnones

1.2.2.1 Synthesis of Münchnones

There are several synthetic methods to obtain münchnones. The cyclodehydration of *N*-acylated α -amino acids **20** is the most common methods to

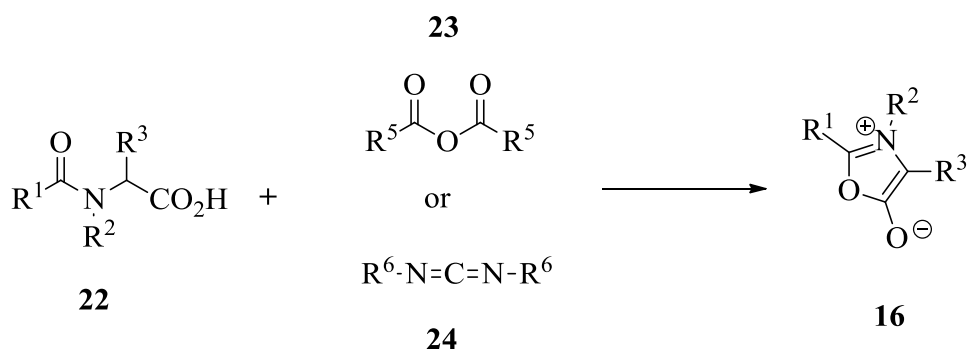
1.2.2.1.1 By Cyclodehydration of Amino Acids



1.2.2.1.1 By Cyclodehydration of Amino Acids

1.2.2.1.1 By Cyclodehydration of Amino Acids

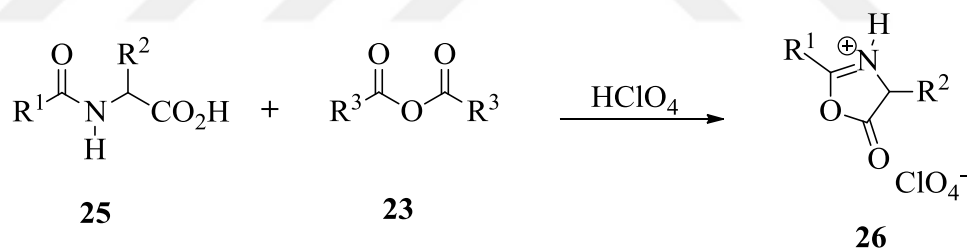
1.2.2.1.1 By Cyclodehydration of Amino Acids



Scheme 1.2.2 Cyclodehydration strategy to form münchnones

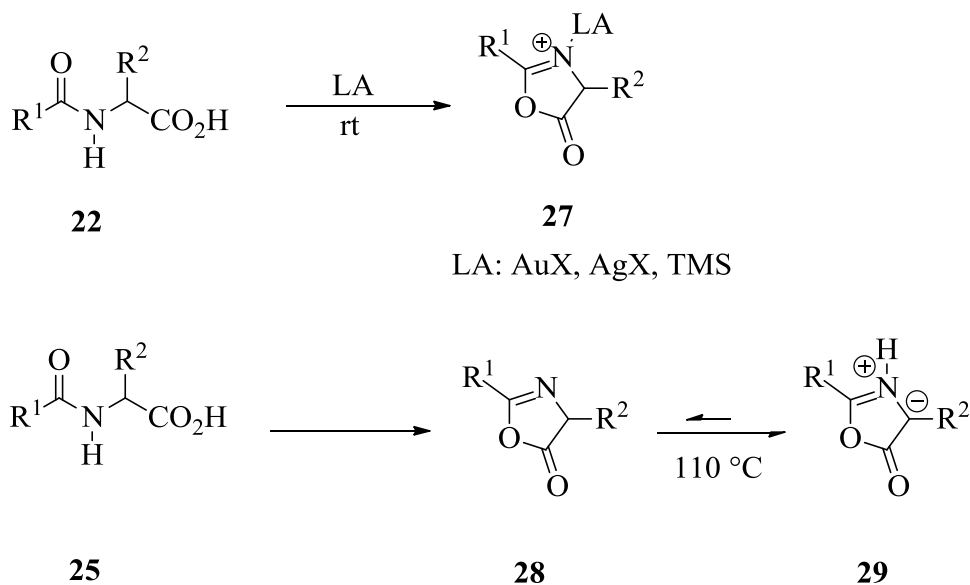
1.2.2.1.2 By Isomerization of Oxazolones

Boyd and Wright were developed another important route to münchnones which involves the cyclodehydration of *N*-acylamino acids **25** with acetic anhydride **23** in the presence of perchloric acid to give *N*-alkylated azlactones **26** (Boyd, 1972, 1972).



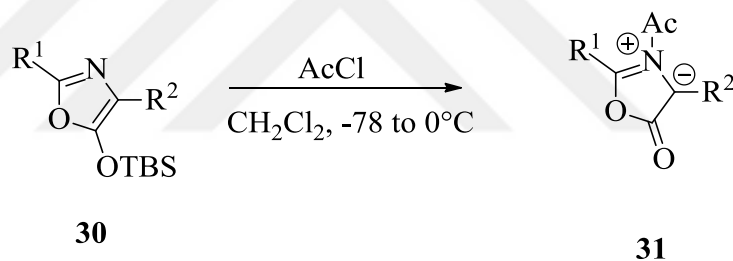
Scheme 1.2.3 Synthesis of 1,3-oxazolonium perchlorates

The mesoionic form of oxazolones **27** or **29** can also be prepared by addition of Lewis acids, Peddibhotla, (2004), upon heating, Matsukubo, (1975), or by the use of metal catalysis (Melhado, 2007).



Scheme 1.2.4 Synthesis of Münchnones from oxazolones

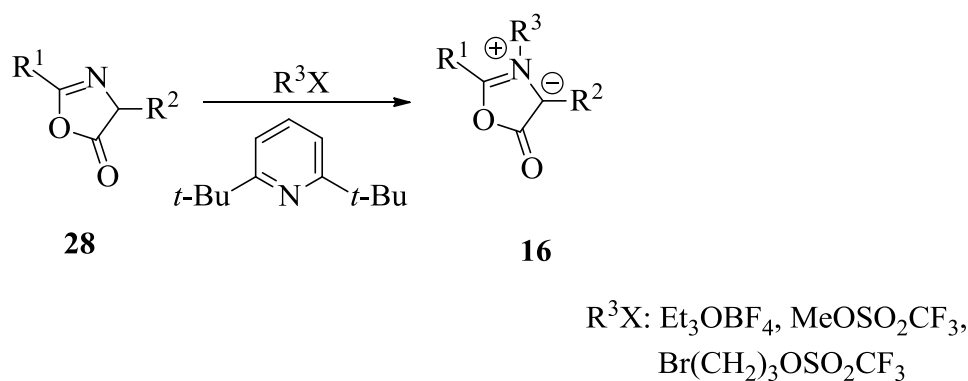
N-acyl münchnone derivatives **31** was generated by Wilde (1988) for the first time via acylation and desilylation of 5-siloxyoxazoles **30**.



TBS: SiMe₂*t*-Bu

Scheme 1.2.5 Generation of Münchnones from 5-siloxyoxazoles

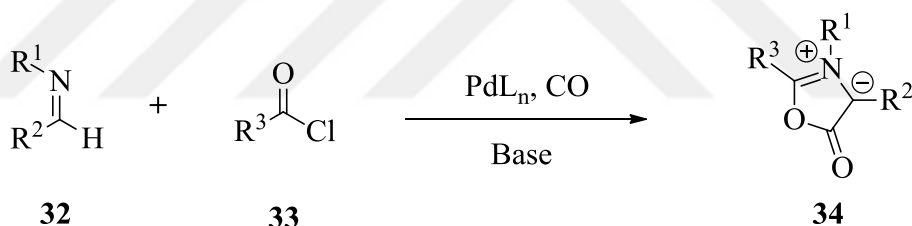
Another method was developed by Hershenson and Pavia (1988) which is producing münchnones **16** *in situ* alkylation of azlactones **28** using deprotonation reagent like 2,6-di-*tert*-butylpyridine.



Scheme 1.2.6 Preparation of Münchnones from *in situ* alkylation of azlactones

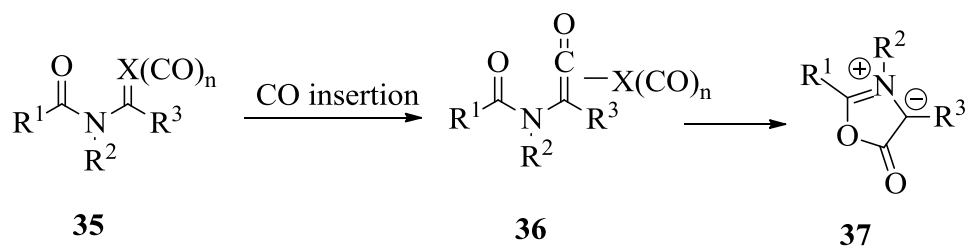
1.2.2.1.3 By Metal-Mediated Routes

Dhawan et al., (2003, 2004) reported the first metal-catalyzed synthesis of münchnone derivatives **34** via the palladium-catalyzed coupling of imines **32**, acid chlorides **33**, and carbon monoxide (CO).



Scheme 1.2.7 Metal-Catalyzed münchnone synthesis

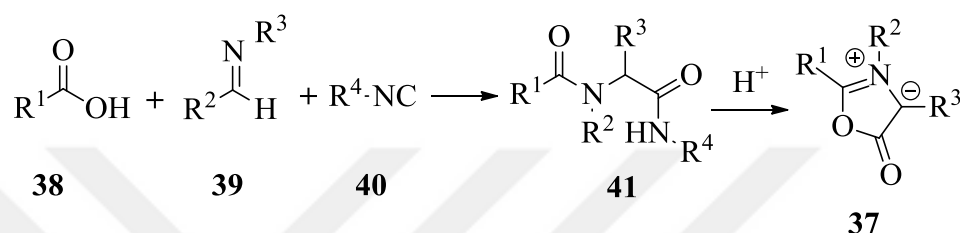
Iron complex **35**, Alper (1979), and chromium carbene complex **35**, Merlic (2000), are reported to behave as precursors to münchnones. These reactions involve the insertion of CO into the chromium carbene bond **36** and latter can cyclize to form Münchnones **37**.



Scheme 1.2.8 Organometallic complexes precursors for münchnone generation

1.2.2.1.4 By Ugi Reactions

The multiple component Ugi reactions are excellent way to provide α -acylaminoamides **41** which can be activated for cyclization to Münchnones **37**. The amido-unit derived from the isocyanide must first be converted to carboxylic acids as precursors for münchnones. On the other hand, the reactive amide groups can be directly converted into münchnone products in the presence of acid (Keating, 1996, and Bienayme, 2000; Strocker and Mjalli, 1996).

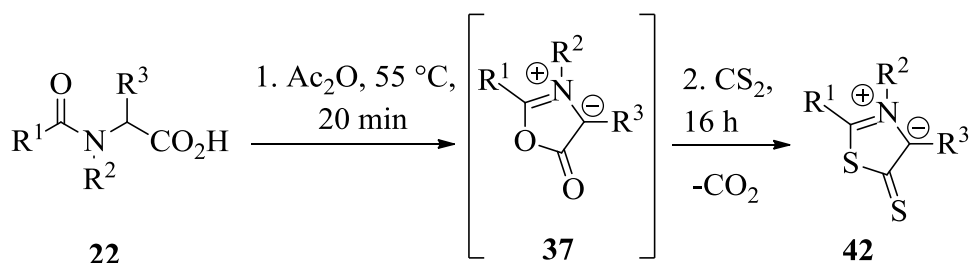


Scheme 1.2.9 Münchnone generation via Ugi adducts

1.2.2.1.5 Other Methods for Preparation of Münchnones

1.2.2.1.5.1 1,3-Thiazolium-5-Thiolates

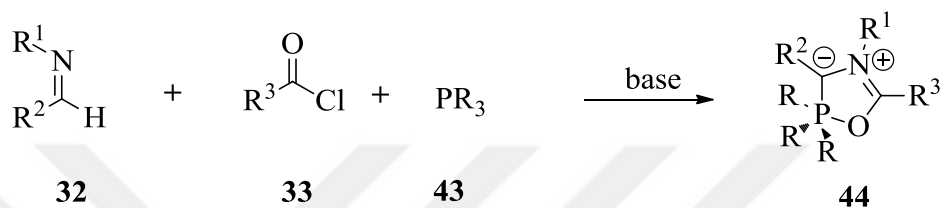
Huisgen (1967) firstly reported that 1,3-thiazolium-5-thiolates **42** could be made by reaction with 1,3-oxazolium-5-olates and since then it has been recognized as a model for the synthesis of mesoionic compounds (Cantillo and Lyra,2010).



Scheme 1.2.10 Synthesis of 1,3-thiazolium-5-thiolates

1.2.2.1.5.2 Phospha-Münchnones

The phospha-münchnones **44** which have also been called montrealones can be generated in one pot, and directly from imines **32**, acid chlorides **33** and PR_3 **43** reagent in the presence of a base. The phospha-münchnones **44** are a new class of 1,3-dipolar cycloaddition precursors that undergoes dipolar cycloaddition with alkynes, or alkenes in analogy to münchnones (Krenske and St. Cyr, 2008; St-Cyr, 2010; Morin, 2013, 2014).

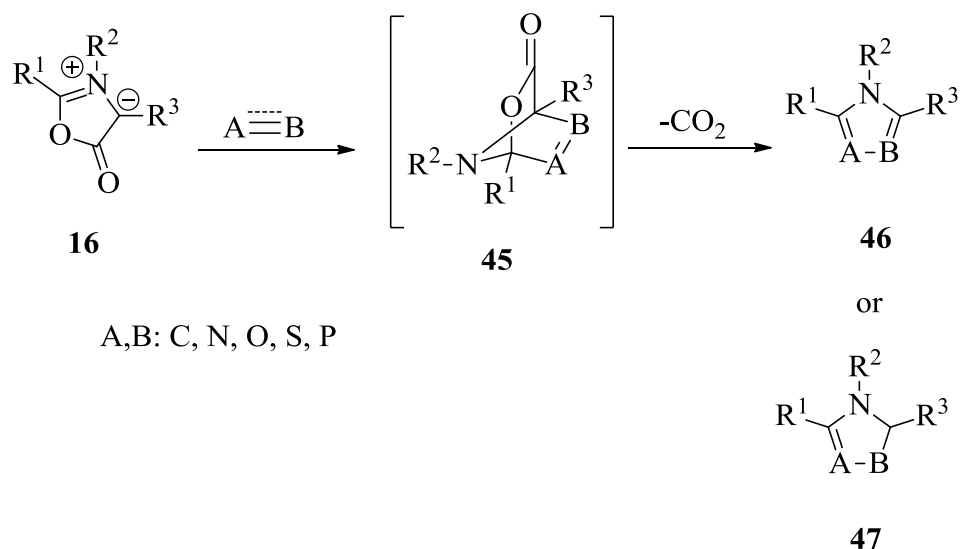


Scheme 1.2.11 Generation of phospha-Münchnones

1.2.2.2 1,3-Dipolar Cycloaddition Reactions of Münchnones and Synthesis of Pyrrole and Pyrrolidine

1,3-Oxazolium-5-oxides, commonly known as münchnones are a special class of azomethine ylides where the 1,3-dipole is integrated into an oxazolium heterocycle that undergo 1,3-dipolar cycloadditions with a broad variety of double and triple bond dipolarophiles, including: alkynes, phosphalkynes, alkenes, aldehydes, imines, thioketones, nitriles, heterocumulenes, nitroso-, nitro-, and aza-compounds.

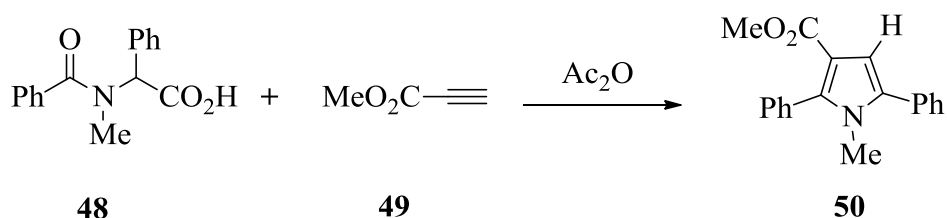
Münchnones **16** are typically used as 1,3-dipolar cycloaddition substrates in the synthesis of pyrrolidines **47** and pyrroles **46** by their in situ generation in the presence of alkenes and alkynes. The münchnone cycloaddition reactions with alkynes efficiently give pyrroles after elimination of carbon dioxide (CO_2).



Scheme 1.2.12 Common cycloaddition products of Münchnones

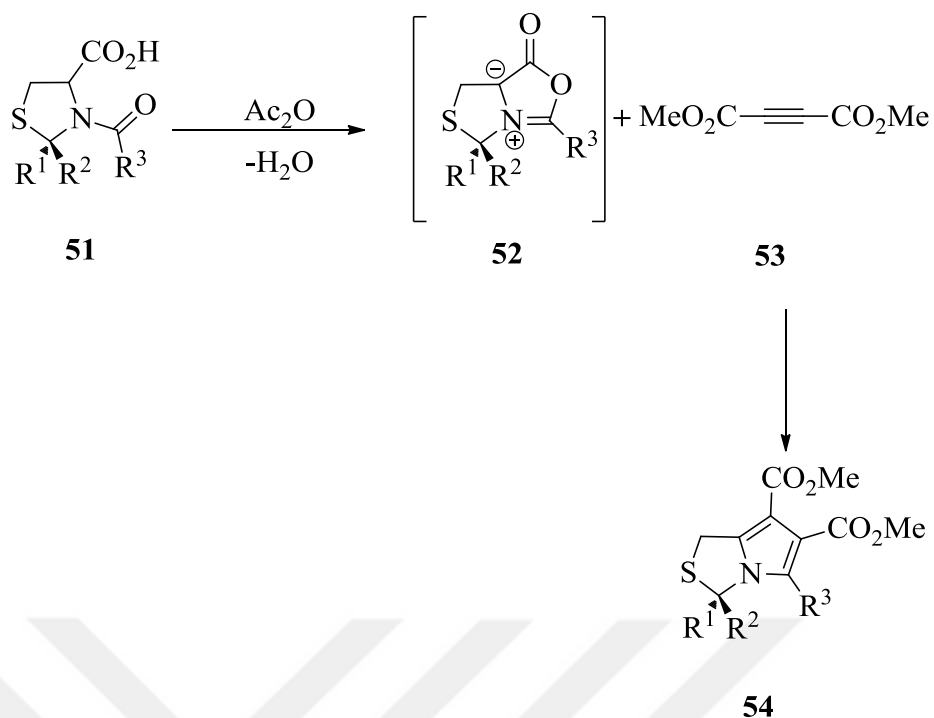
1.2.2.2.1 Synthesis of Pyrrole Derivatives

Huisgen and coworkers, (1964a), (1964b) demonstrated the first example of pyrroles in 1,3-dipolar cycloadditions by cyclodehydration of amino acid **48** to münchnone with acetic anhydride and addition of methyl propiolate **49**.



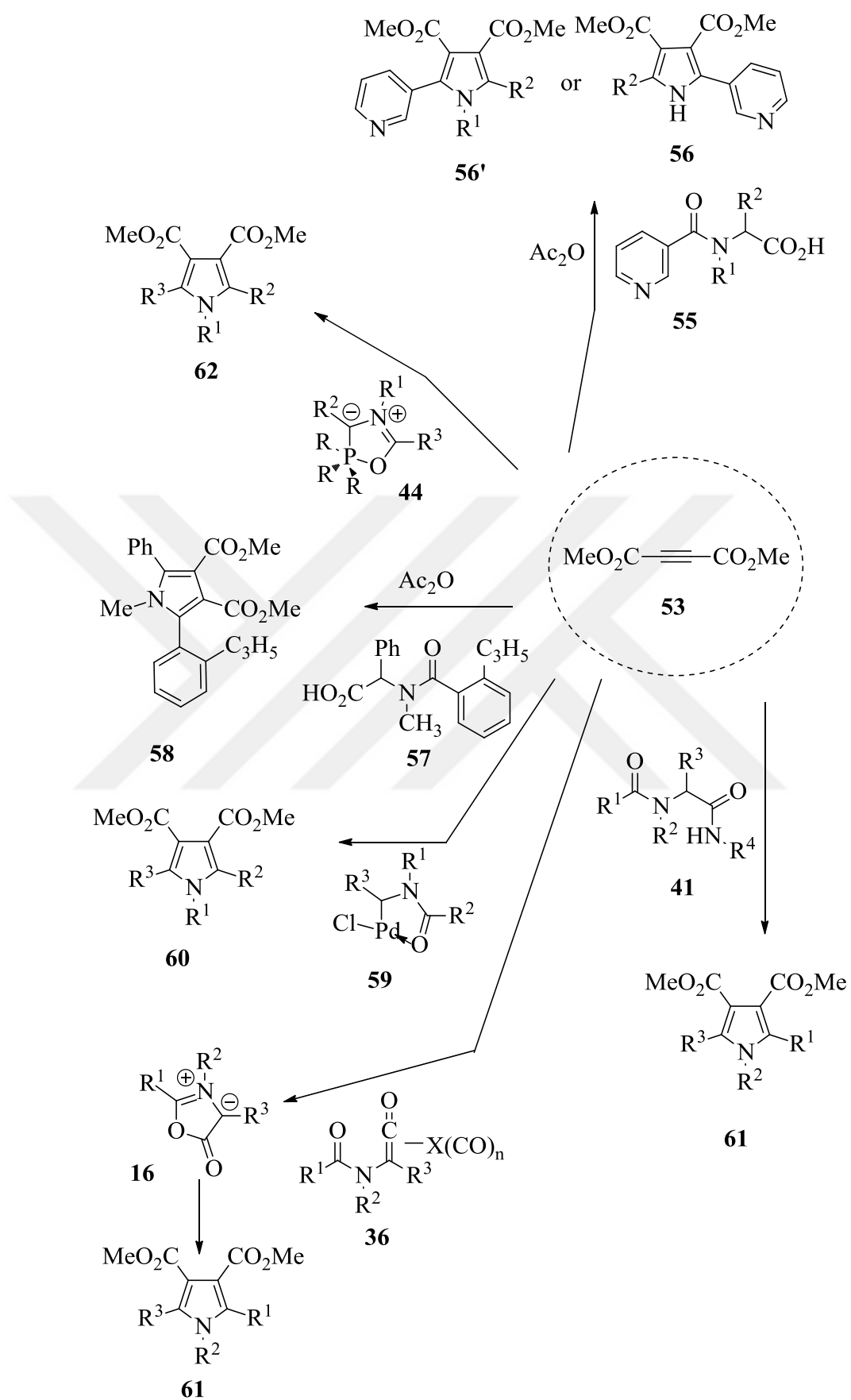
Scheme 1.2.13 1,3-dipolar cycloaddition of Münchnone with methyl propiolate

Dimethylacetylenedicarboxylate (DMAD) **53** is a powerful and reliable dipolarophile that is used to synthesize various pyrrole derivatives with münchnones. Cycloaddition reaction of 2-substituted-*N*-acylthiazolidine-4-carboxylic acids **51** which used to generate 5*H*,7*H*-thiazolo[3,4-*c*]oxazolium-1-olates **52** with dimethylacetylenedicarboxylate (DMAD) **53** furnish 1*H*-pyrrolo[1,2-*c*]thiazole derivatives **54** (Pinho e Melo, 1999).



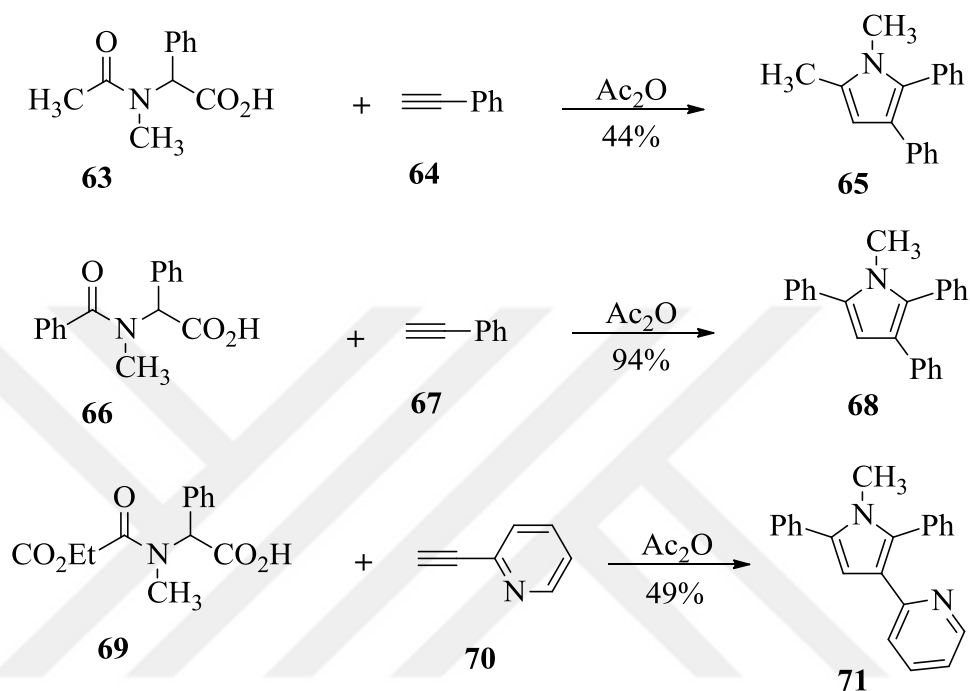
Scheme 1.2.14 Cycloaddition of Münchnone with DMAD

The münchnone generation-DMAD trapping protocols are efficient methods, because of the highly reactive DMAD can allow even the least stable and least reactive münchnones, to furnish various pyrrole derivatives (Harju, 2009; Padwa, 1982; Dhawan, 2003 and 2004; Alper, 1979; Merlic, 2000; Keating, 1996; Bienayme, 2000; Strocker and Mjalli, 1996; Krenske and St. Cyr, D. J, 2008).



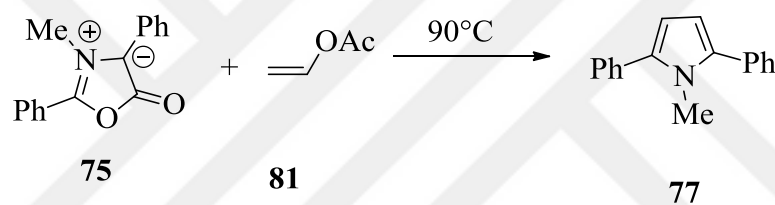
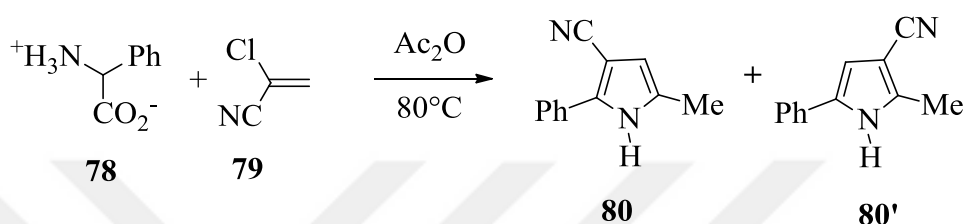
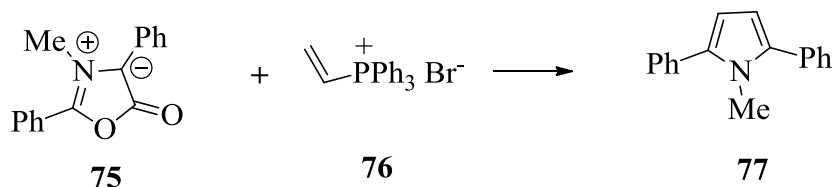
Scheme 1.2.15 Synthesis of some pyrrole derivatives using variety of Müchnones

Electron poor alkynes react most rapidly with münchnones instead of electron rich alkynes. Münchnones have numerous substitution variants, which can influence the stability and reactivity of münchnones. Depending on the replacement of substituent of 1,3-dipoles, the cycloaddition yield of münchnones with arylacetylenes **64**, **67** and **70** decreases (Groce, 1988; Potts, 1979).

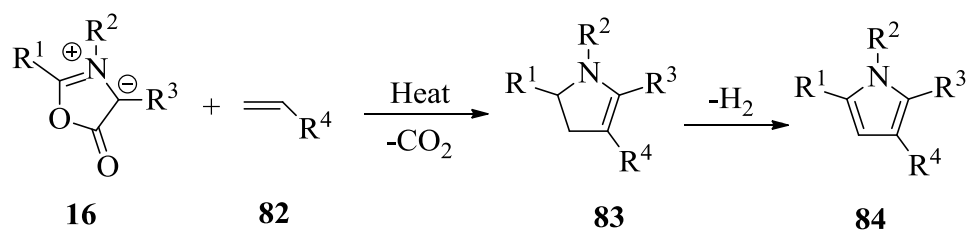


Scheme 1.2.16 Substituent effects on Münchnone formation and reactivity

Münchnone-Alkene cycloadditions can also lead to pyrrole formation via HX elimination. These alkenes involve electron-withdrawing leaving groups $\text{CH}_2=\text{CHX}$ such as OAc **81**, Gotthardt (1970), Cl **79**, Benages (1978), NO_2 **72**, Gribble (1998), CN **79**, Dhawan (2003) and $\text{PPh}_3^+\text{Br}^-$ **76** (Clerici, 1998).

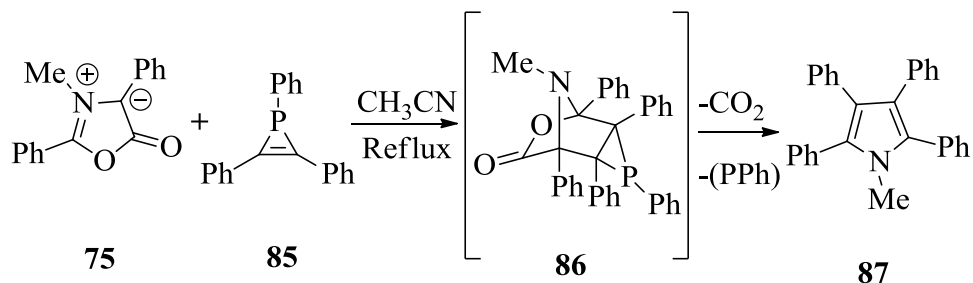


Alkenes without leaving groups react with münchnones, which can undergo spontaneous oxidation to generate pyrroles. For example, the cycloaddition of styrene, 1-hexene **82** with münchnones **16** at elevated reaction temperatures results in spontaneous oxidation to furnish the corresponding pyrroles **84** (Padwa, 1982; Pinho e Melo, 2000, 2002).



16

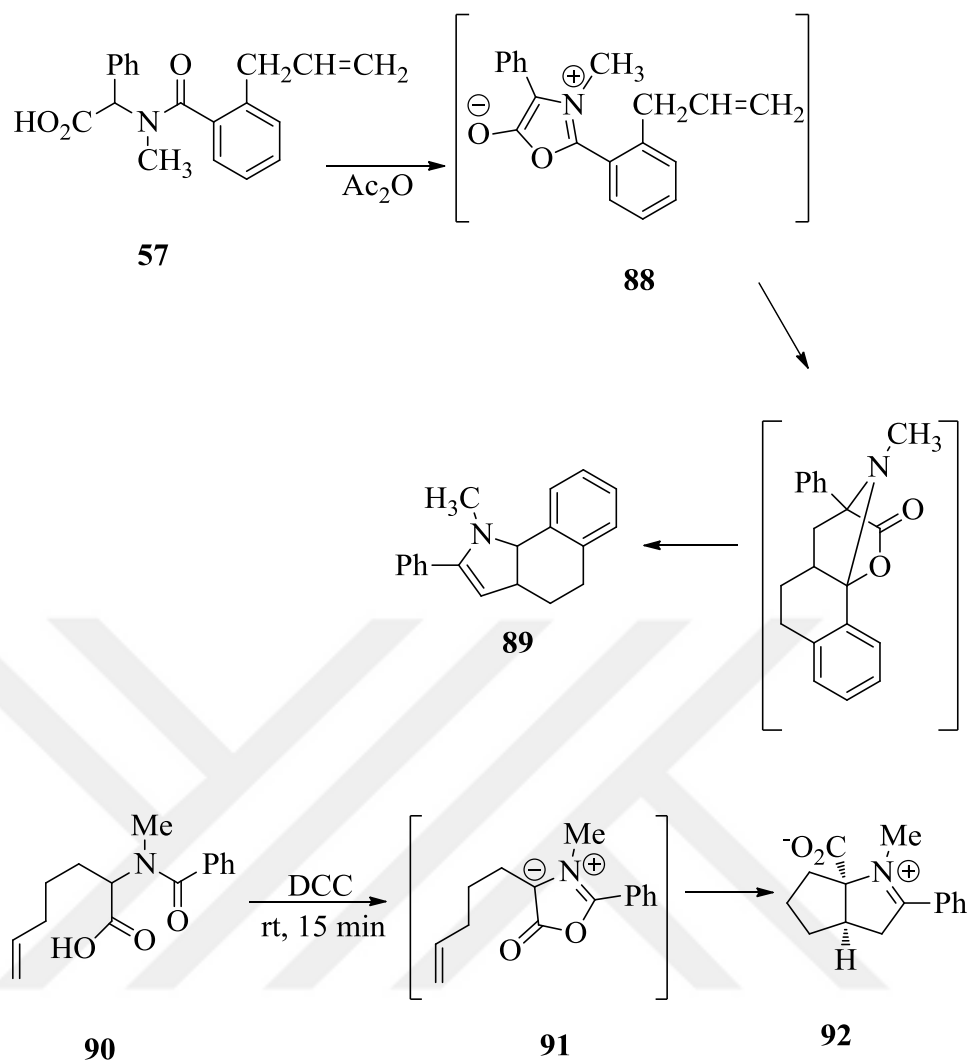
Kobayashi and co-workers (1995) used unusual dipolarophile which was 1,2,3-triphenyl-1*H*-phosphirene **85** reacted with münchnone **75** to furnish 1-methyl-2,3,4,5-tetraphenylpyrrole **87**.



Scheme 1.2.19 Cycloaddition of Münchnones and unusual dipolarophile

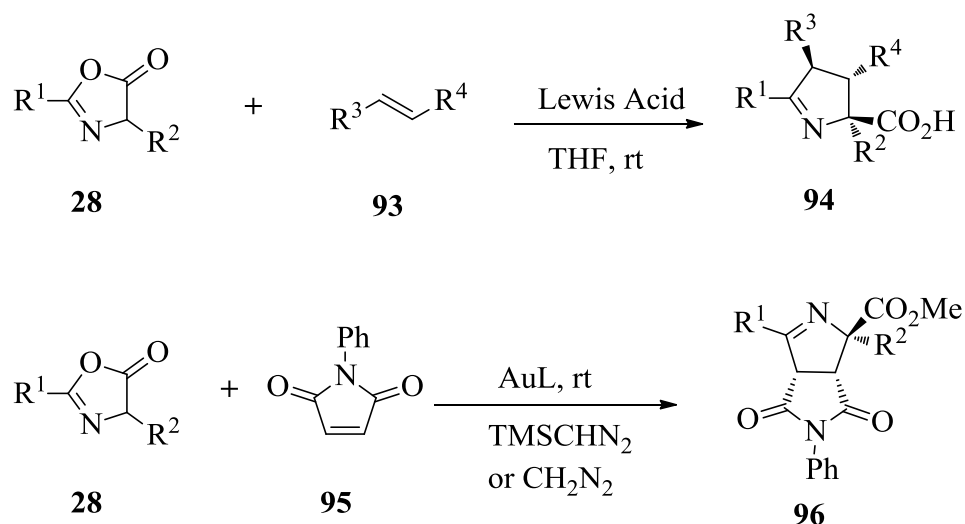
1.2.2.2.2 Synthesis of Pyrroline Derivatives

1,3-Dipolar cycloaddition reactions of münchnones, behaving like a azomethine ylide, with various alkenes provides pyrroline derivatives. Padwa and co-workers (1982) synthesized pyrroline derivatives **89** with intramolecular cycloaddition of *N*-alkyl münchnones **88**. Belanger *et al.* (2007) also investigated a path of intramolecular 1,3-dipolar cycloaddition of münchnones, to give zwitterionic pyrroline carboxylate **92**.



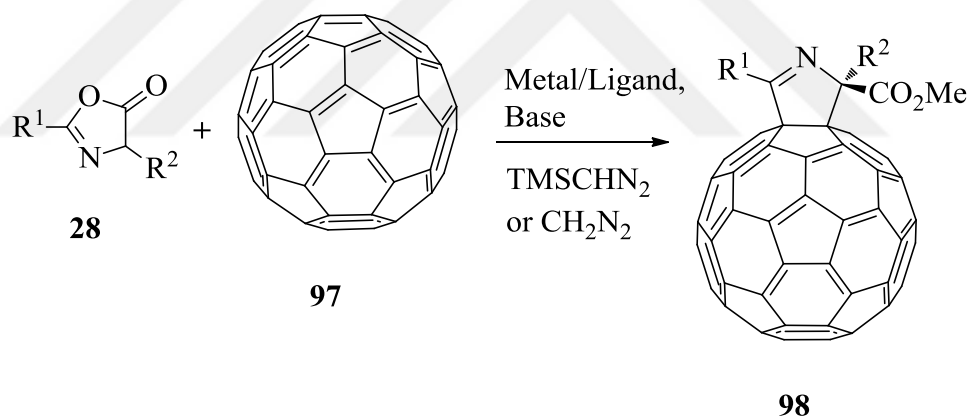
Scheme 1.2.20 Synthesis of pyrrolines *via* intramolecular alkene cycloaddition.

Peddibhotla (2002, 2003, 2004) and Sharma (2005) reported Lewis acid catalyzed 1,3-dipolar cycloaddition of azlactones **28** with alkenes **93** to generate pyrroline carboxylates derivatives **94**. Melhado also reported (2007) enantioselective gold-catalyzed cycloaddition of azlactones **28** and alkenes **95** to furnish chiral pyrroline carboxylates **96** in high enantiomeric excess.



Scheme 1.2.21 Lewis acid and gold catalyzed-mediated synthesis of pyrrolines

Martinez and co-workers (2004) published the first organocatalytic where the oxazolones **28** are used as 1,3-dipoles (the so-called münchnones) with fullerenes **97** to obtain pyrrolino[60]fullerene derivatives **98** with good enantiomeric excesses.

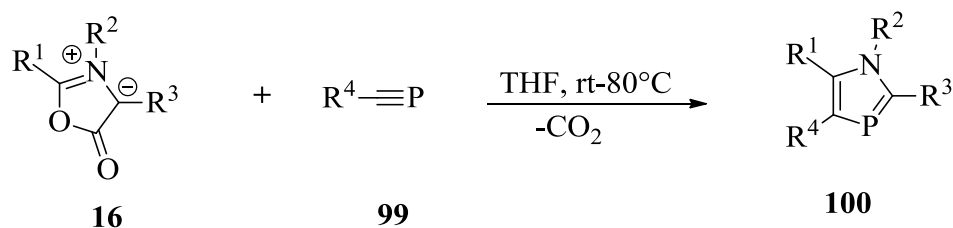


Scheme 1.2.22 Synthesis of pyrroline with azlactone and fullerene

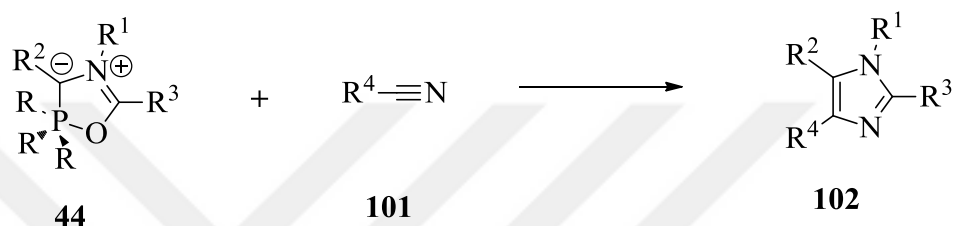
1.2.2.2.3 Reactions of Hetero-Dipolarophiles with Münchnones

The cycloaddition reactions of münchnones with heterodipolarophiles to provide several aromatic heterocycles. The electron rich phosphalkynes **99** which are most effective dipolarophiles were used cycloaddition with münchnones to furnish phosphazole products **100** (Mack, 1998; Markl, 1986). In contrast to the

electron rich phosphalkynes, electron poor nitriles **101** were used a substrate for the cycloaddition with münchnones to give imidazole derivatives **102** (Aly, 2015).

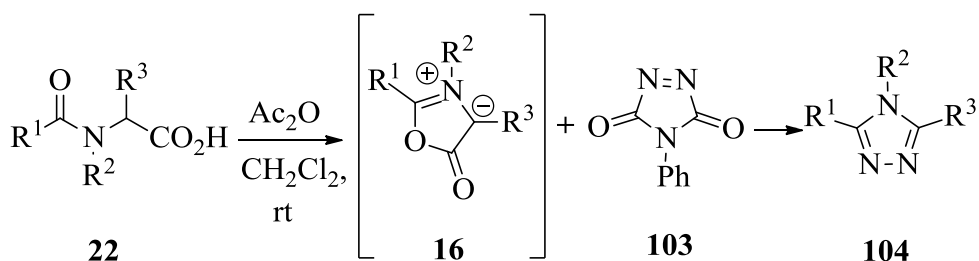


Scheme 1.2.23 Cycloaddition reaction of Münchnone with phosphalkyne



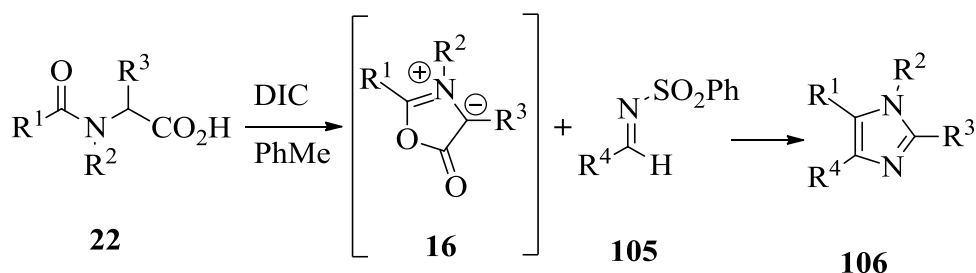
Scheme 1.2.24 Synthesis of imidazoles via phosphamünchnone cycloaddition with nitrile

Swapn (2005) demonstrated that 4-phenyl-4*H*-1,2,4-triazoline-3,5-dione **103** reacted with münchnones **16** furnish 1,2,4-triazole derivatives **104**.



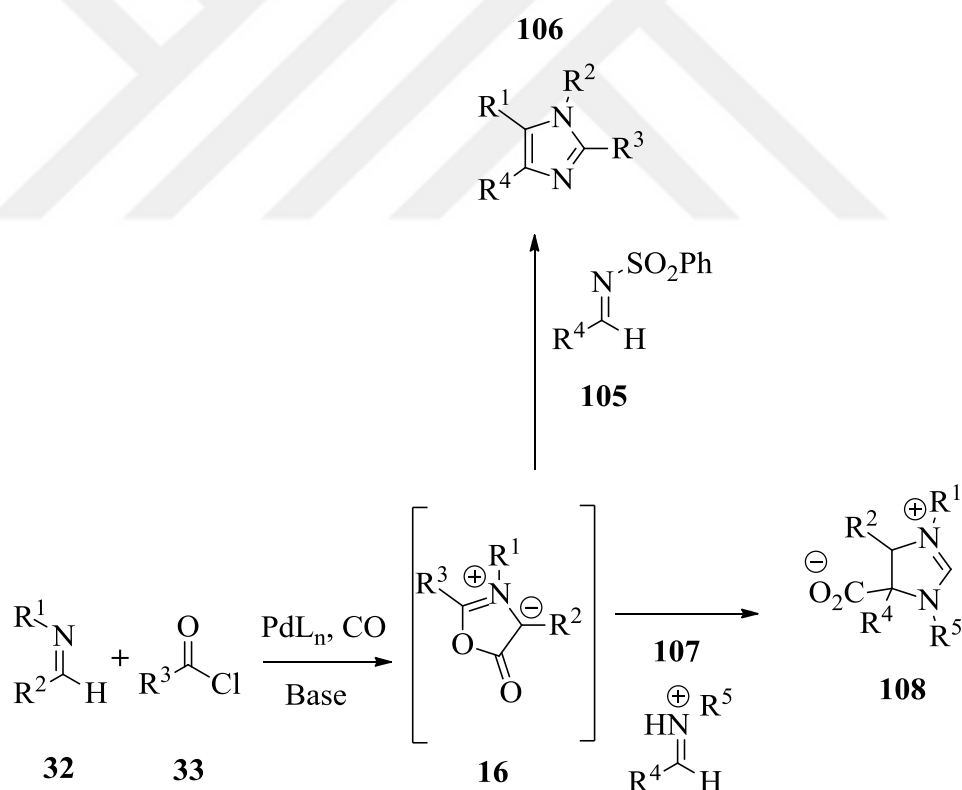
Scheme 1.2.25 Preparation of the 1,2,4-triazoles via 1,3-oxazolium-5-olates (Münchnones)

Imines **105** can also act as dipolarophiles in 1,3-dipolar cycloaddition reactions with münchnones. Consonni et al. (1991) firstly reported 1,3-dipolar cycloaddition reactions of münchnones **16** with imines **105** to furnish poly substituted imidazole derivatives **106**.



Scheme 1.2.26 Synthesis of imidazole from Münchnone/imine cycloaddition

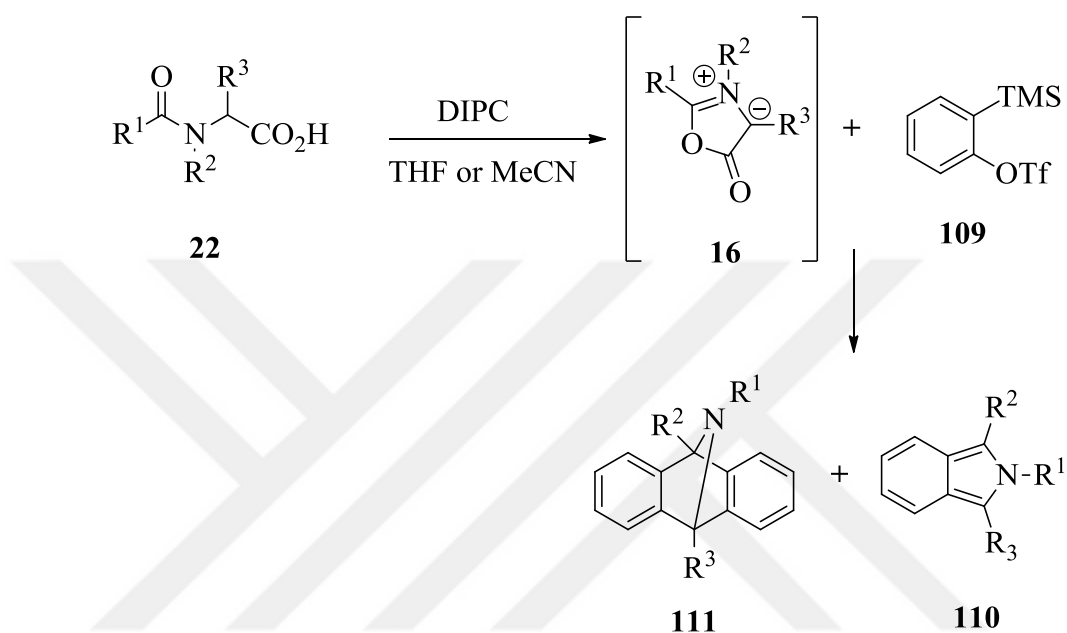
Dghaym (2001) and Dhawan (2004) reported that münchnones can be synthesized *via* the palladium-catalyzed multicomponent coupling of acid chlorides **33**, imines **32** and carbon monoxide. These dipoles display similar reactivity to münchnones and undergo cycloaddition with *N*-alkyl and *N*-aryl imines, protonated imines **107** and *N*-tosyl imine **105** to give imidazolium carboxylate **108** and tetra-substituted imidazole derivatives **106**.



Scheme 1.2.27 Cycloaddition reactions of palladium-catalyzed Münchnones with imines

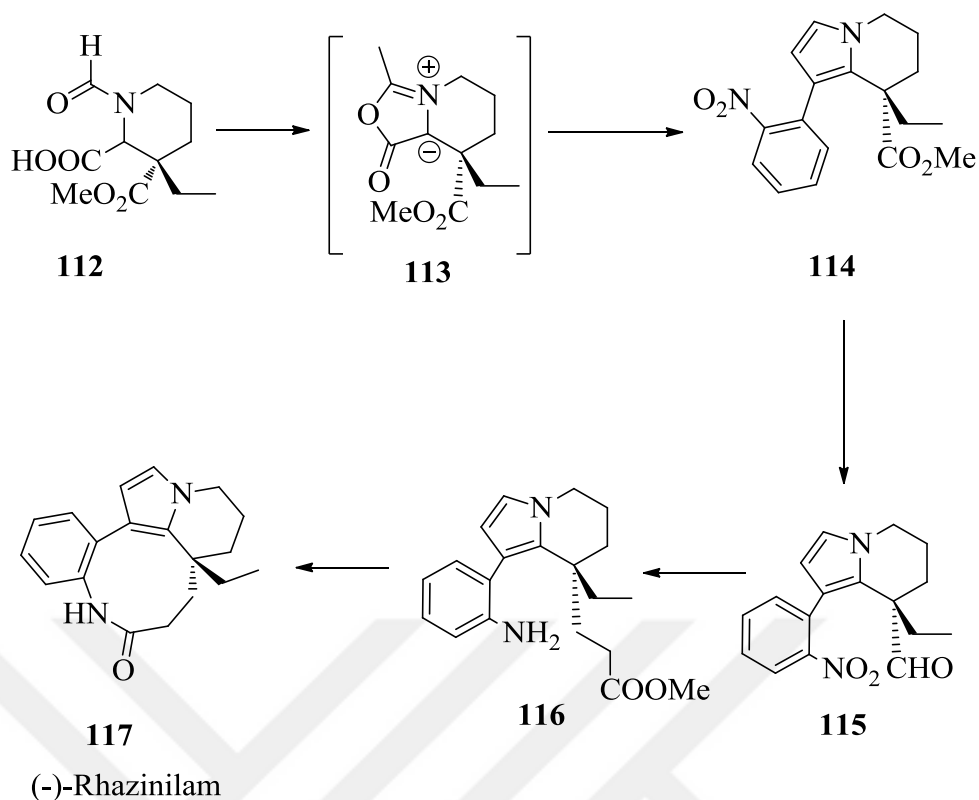
1.2.2.2.4 Recent Applications for 1,3-Dipolar Cycloaddition Reactions of Münchnones

Münchnone precursors **22** cyclized in situ by treatment with *N,N'*-diisopropylcarbodiimide (DIPC) with unsubstituted aryne precursor **109** was reported by Gribble et al. (2014) to furnish isoindole **110** and benzathracenimine **111**.



Scheme 1.2.28 Reaction of arynes with Münchnones

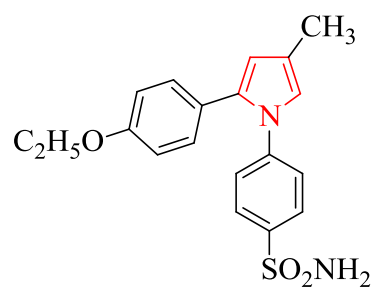
Sugimoto et al. (2014) achieved total synthesis (-)-rhazinilam **117** using 1,3-dipolar cycloaddition reaction of the highly elaborated münchnone **113** generated from *N*-formyl pipecolic acid **112**.



Scheme 1.2.29 Synthesis of (-)-Rhazinilam

1.2.2.2.5 Biological Importance of Pyrrole Derivatives

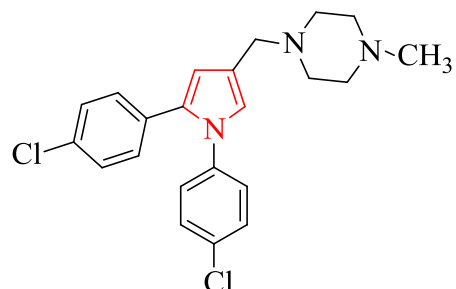
The pyrrole core is found a wide range of natural and non-naturally occurring compounds and bioactive molecules, including anti-inflammatory **118** (CS-706), Ushiyama (2008), antimycobacterial agents **119** (BM212), Biava (2009), and the blockbuster drug Atorvastatin (Lipitor) **120** (Chong, 1997).



118

CS-706

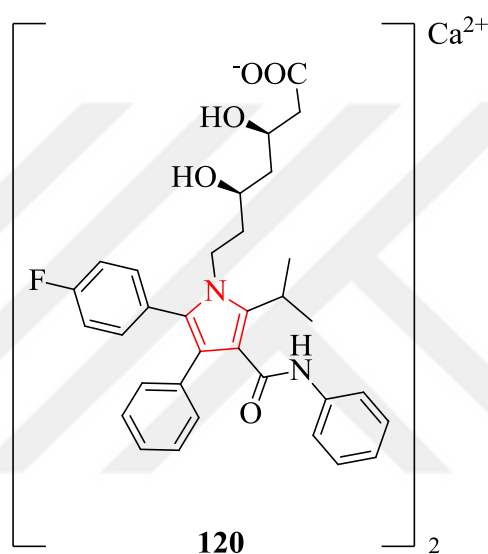
anti-inflammatory agent



119

BM212

antimycobacterial agent

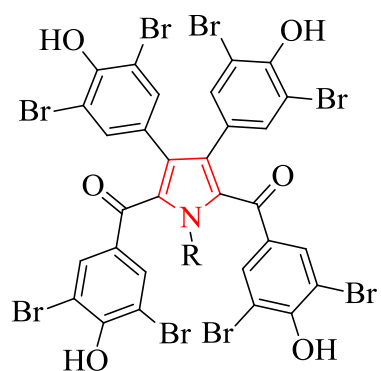


120

Atorvastatin

Figure 1.2 2 Some of the non-naturally biologically important pyrroles

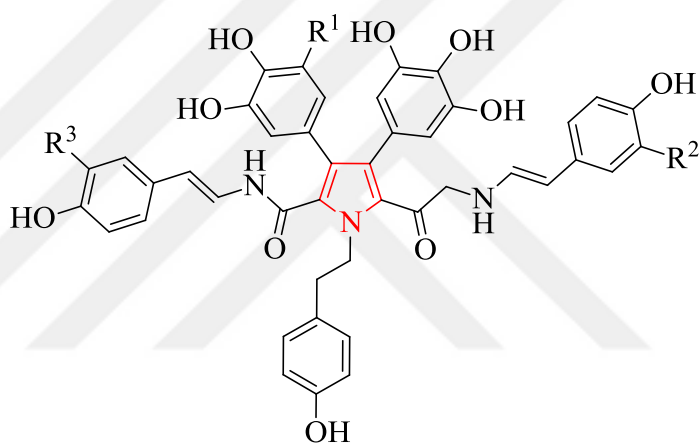
The natural products of storniamides A-D **122**, Palermo (1996), in which the main core is pyrrole is a potent antibiotics and the polycitone A **121**, Loya (1999), is a general inhibitor of cellular DNA polymerase.



121

Polycitone A

R: CH₂-C₆H₄-4-OH



122

Storniamide

A: R¹: OH, R²=R³: H

B: R¹=R³: OH, R²: H

C: R¹: H, R²=R³: OH

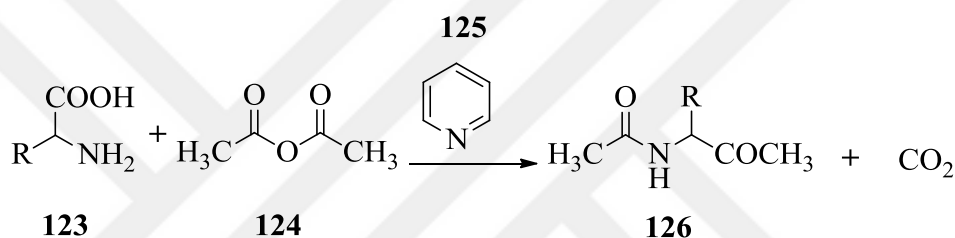
D: R¹=R²=R³: H

Figure 1.2 3 Structure of polycitone A and storniamides A-D

1.3 CHAPTER 3

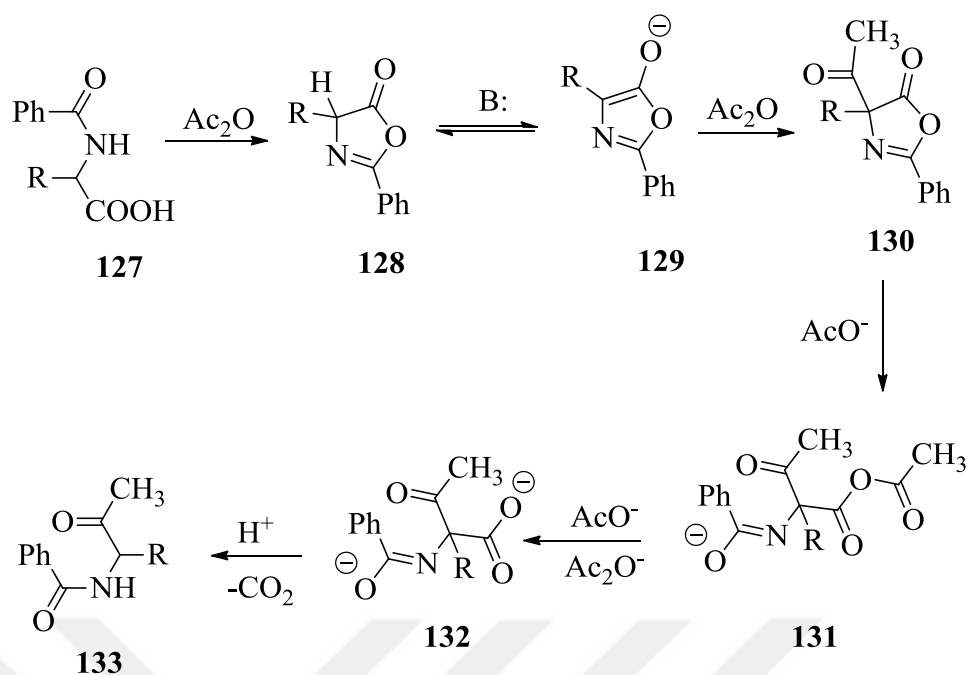
1.3.1 Dakin West Reaction

Dakin and West (1928), firstly reported the reaction of an α -amino acid **123** with acetic anhydride **124** in the presence of a base **125** to furnish α -acetamidoalkyl methyl ketone **126**. This reaction is a well-known procedure for the preparation of especially α -acetamido methyl and β -aryl ketones which are important skeletons of biologically or pharmacologically important compounds (Casimir, 1995).



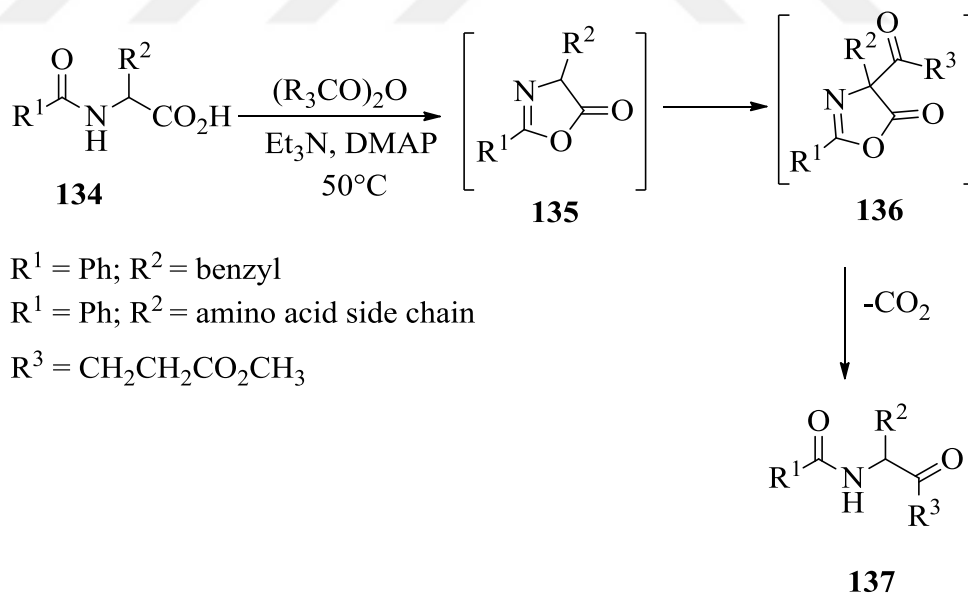
Scheme 1.3.1 Synthesis of α -acetamido methyl ketone

Dakin and West (1928), proposed the first azlactone type mechanism which is the most favored one. The mechanism of Dakin-West reaction has been studied by many chemists (Rondestvedt, 1950; Iwakura, 1967; Korman, 1974). The reaction of α -amino acid **127** and acetic anhydride occur via a cyclic intermediate, oxazolones **128**. The base deprotonate oxazolones to form a reactive anion which undergoes condensation with acetic anhydride. Then ring opening occurs with anion to form **131** which undergoes deacetylation and decarboxylation under this reaction conditions.



Scheme 1.3.2 Mechanism of Dakin-West type reactions

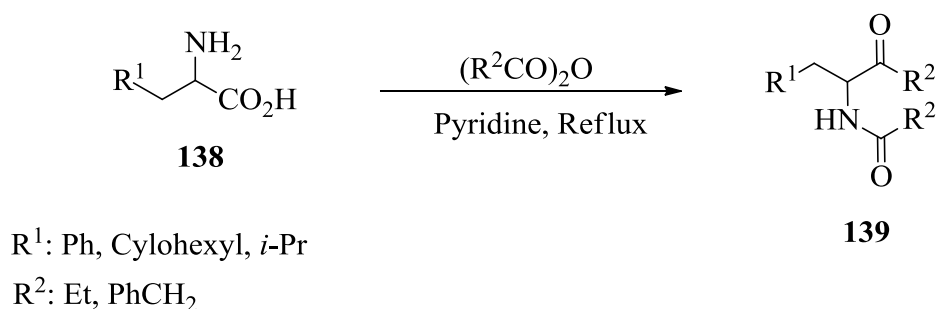
McMurray and co-workers, (1985) modified a method to synthesize ketomethylene derivatives. Dakin-West procedure was used to convert *N*-benzoyl amino acids **134** directly to their ketopropionates **137** in a single preparative step.



Scheme 1.3.3 Preparation of ketomethylene peptide analogues

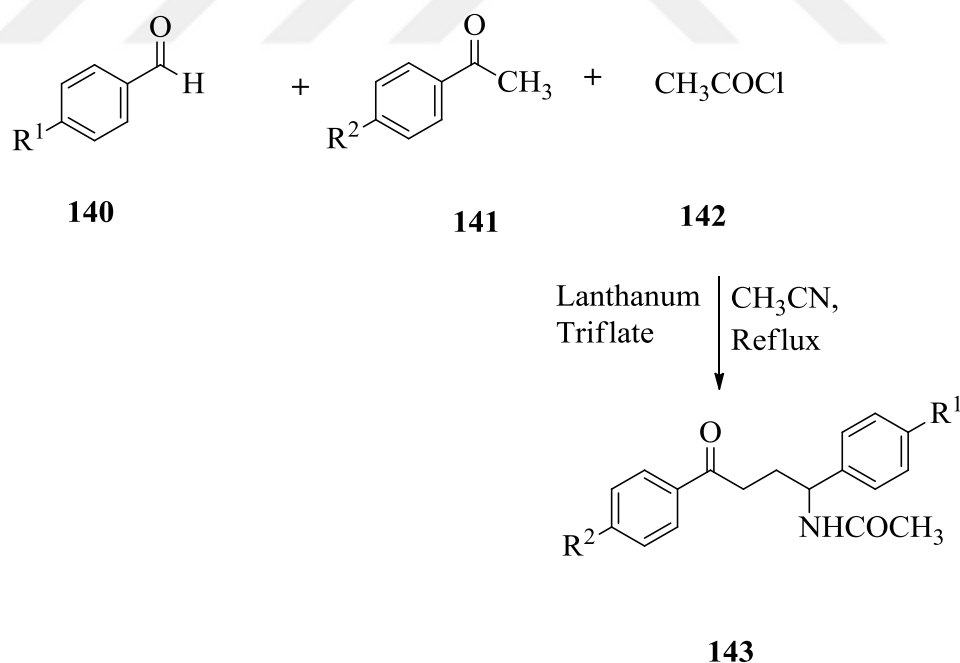
Different analogues of Capravirine AG-1549 or S-1153 were synthesized from corresponding amino acids. Dakin-West type reaction which was a part of procedure was applied on amino acids by refluxing them with a mixture of

phenylacetic acid **138**, anhydride and pyridine to afford derivatives of acetamide **139** (Loksha, 2005).



Scheme 1.3.4 Synthesis of acetamide

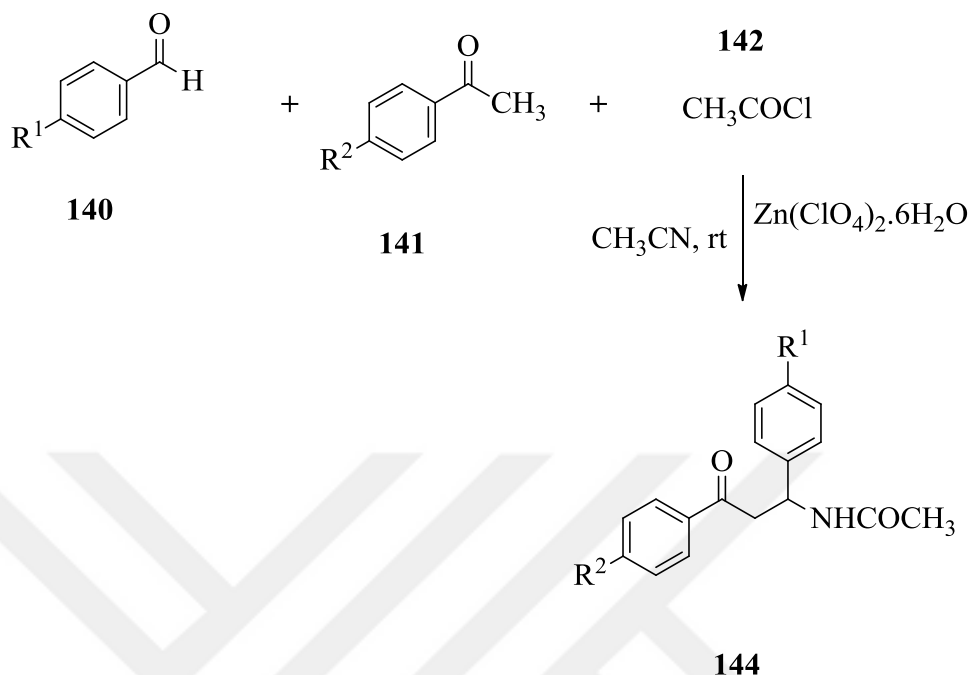
The derivatives of Dakin-West reaction of acetamido ketones were prepared by a mixture of benzaldehyde **140**, acetophenone **141**, acetyl chloride **142** and acetonitrile in the presence of lanthanum triflate as a catalyst was stirred under various reaction conditions. This method is a new and simple synthetic method to furnish β - acetamido ketones **143** by coupling four components in the presence of a solid catalyst (Tiwari, 2008).



Scheme 1.3.5 Solid catalyst Dakin-West reaction of acetamido ketones

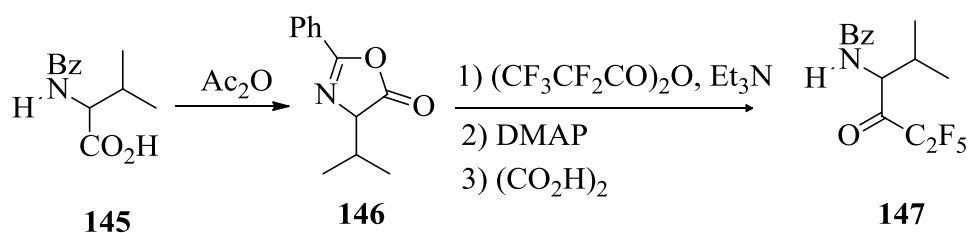
The other route for modification of Dakin-West reaction is described in another study, which involves the reaction of mixture of acetophenone **141**,

benzaldehyde **140**, acetyl chloride **142**, and acetonitrile in the presence of various metal triflates and perchlorates to afford *N*-(3-oxo-1,3-diphenylpropyl) acetamide **144** at room temperature (Nepali, 2011).



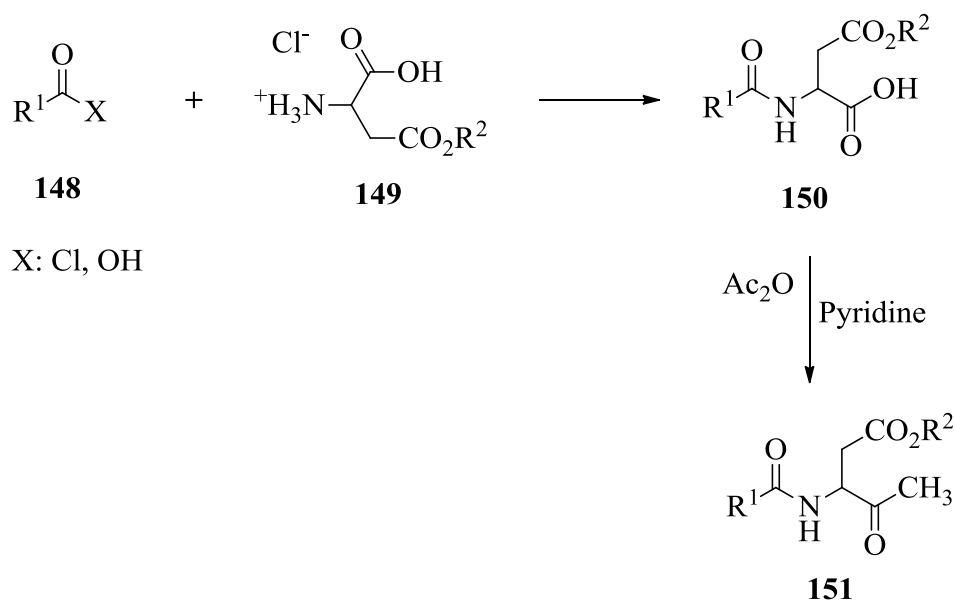
Scheme 1.3.6 Metal catalyst modified Dakin–West condensation

Curran, (1995) used the implementation of the Dakin-West procedure to prepare α -amino-pentafluoroethyl ketone derivatives **147** starting with *N*-benzoyl valine **145**.



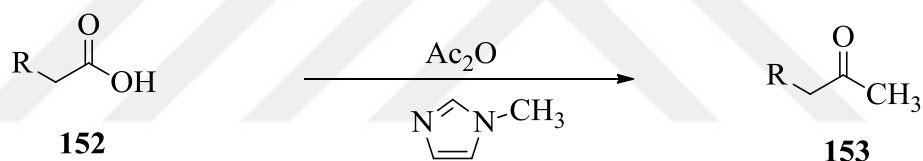
Scheme 1.3.7 Synthesis of perfluoro ketone

The other application of Dakin-West reaction was used to convert amino acids **150** to keto-amide **151** to provide the central oxazole ring. This method was useful for the synthesis of a wide variety of oxazole-containing dual PPAR α/γ agonists (Godfrey, 2002).



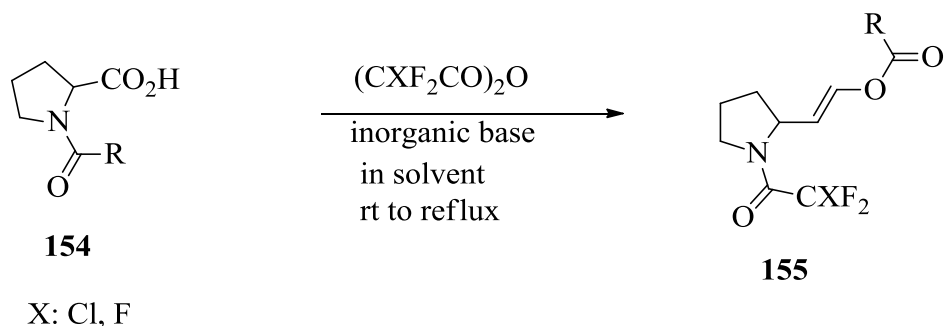
Scheme 1.3.8 Synthesis of compound **151**

A series of β-aryl ketones **153** were synthesized by Tran et al., (2006) with Dakin-West reaction of carboxylic acids **152** with 1-methylimidazole as a catalyst was stirred at room temperature.



Scheme 1.3.9 Dakin-West reaction of carboxylic acid

Saeki and co-workers (2009), investigated Dakin-West type reaction of *N*-acylprolines **154** with chlorodifluoroacetic anhydride (CFAA) or trifluoroacetic anhydride (TFAA) in the presence of inorganic bases as catalysts to furnish enol ester derivatives **155**.



Scheme 1.3.10 The Dakin-West reaction of *N*-acylprolines with inorganic base

1.4 CHAPTER 4

1.4.1 N-Acylurea

The *N*-acyl urea derivatives are an important class of substrates for the medicinal and agrochemical applications. Cabergoline **156**, Brambilla (1989), which is the dopamine D2 agonist was used an *anti* Parkinson's agent in 1993. In addition, *N*-acylurea derivatives were synthesized and used as inhibitors of the reproduction and growth for the house fly **158** and fall army worm **157** (DeMilo, 1978).

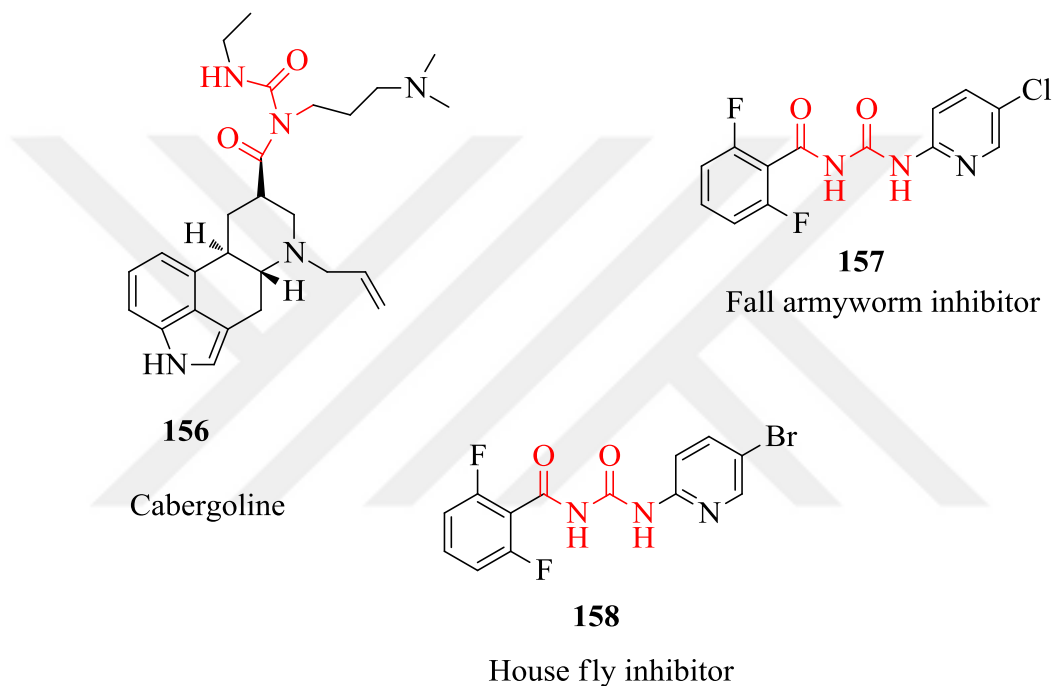
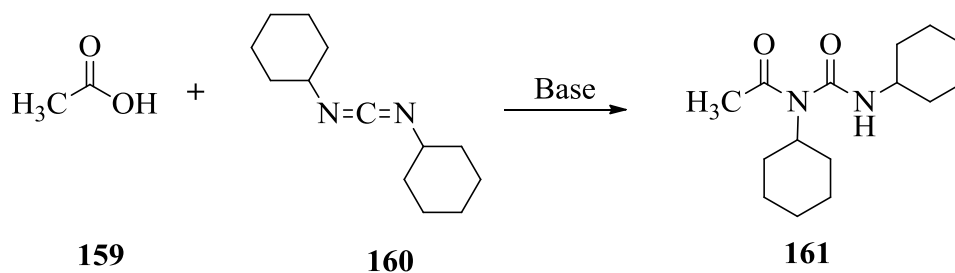


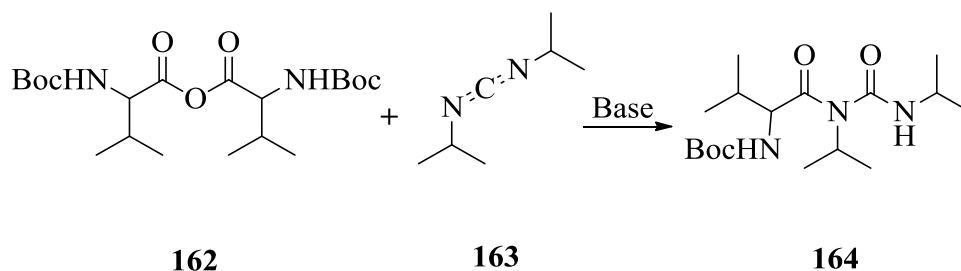
Figure 1.4.1 Structure of Cabergoline, inhibitors of fall armyworm and house fly

De Tar and Silverstein (1996) reported the mechanisms of the reactions of carbodiimides **160** with carboxylic acids **159** in the presence of bases at higher temperatures to furnish *N*-acylurea derivatives **161**.



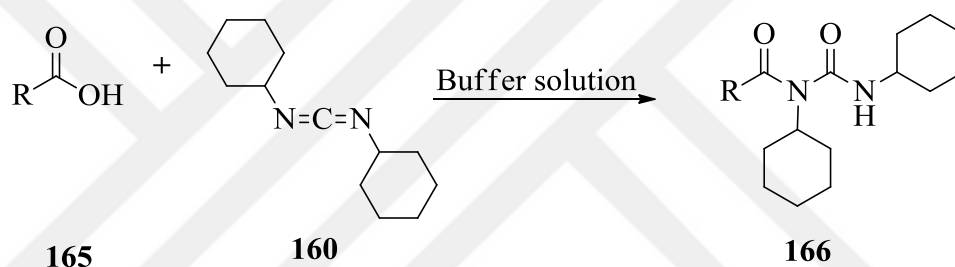
Scheme 1.4.1 Reaction of acetic acid with carbodiimide

The reaction of *N,N*-diisopropylcarbodiimide **163** with symmetrical anhydrides of BOC-protected amino acids **162** gave high yields of *N*-acylureas **164** (Benoiton, 1981).



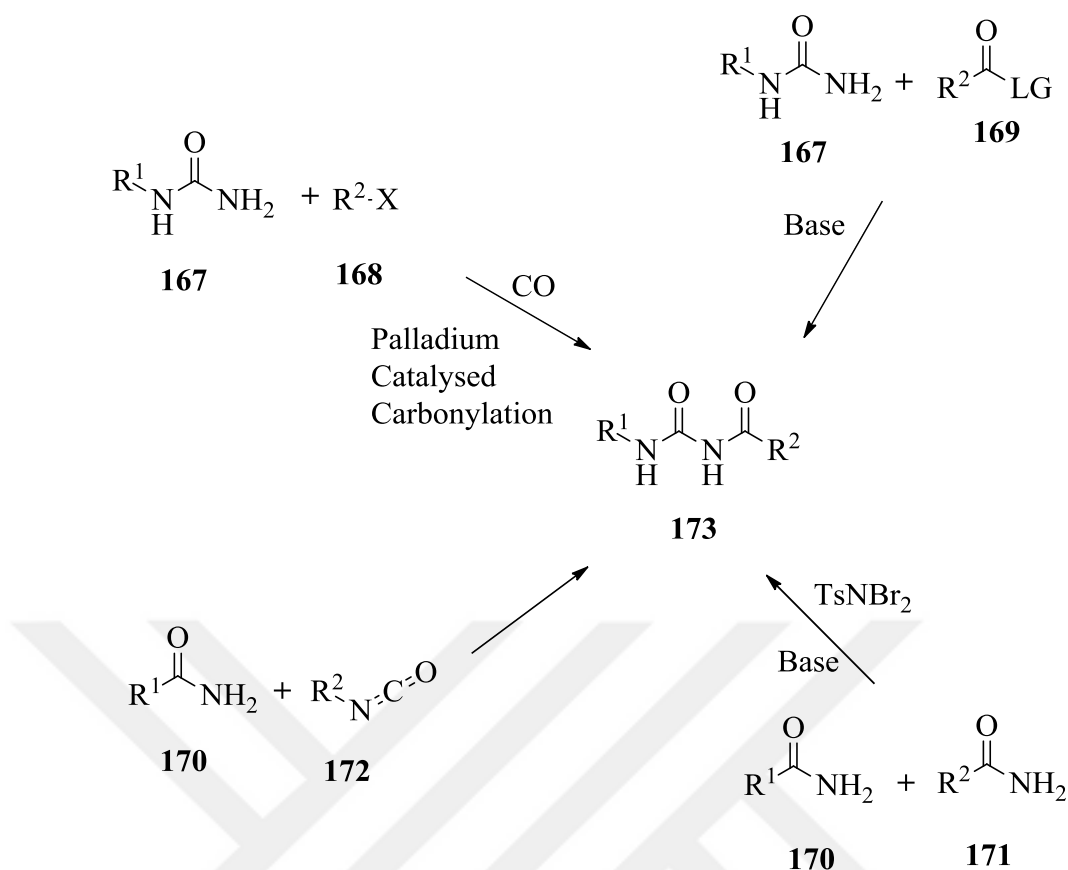
Scheme 1.4.2 Formation of compound **164**

The reaction of *N,N*-dicyclohexylcarbodiimide **160** with substituted benzoic acids **165** in the presence of buffer solution were shown in 1995 to afford *N*-acylurea derivatives **166** (Slebiada, 1995).



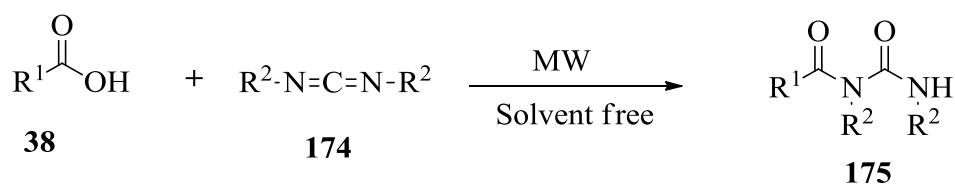
Scheme 1.4.3 Synthesis of *N*-acylurea derivatives in the presence of buffer solution

The reaction between an amide **170** and isocyanate **172**, reaction of substituted ureas **167** with acids or acyl chlorides **169** at elevated temperature, transition-metal-catalyzed carbonylation and carboxamides **170** and in situ generated isocyanates (from *N,N*-dibromo-*p*-toluenesulfonamide) in the presence of a base are other strategies to obtain *N*-acylureas (Bjerglund, 2012; Liptrot, 2010; Wiley, 1949; Singh, 2013).



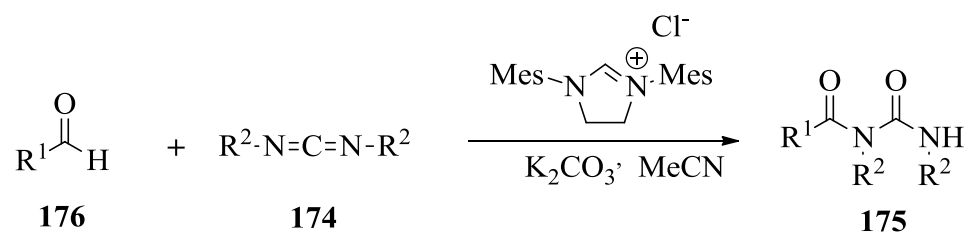
Scheme 1.4.4 The methods for the preparation of *N*-acylureas

In a microwave-assisted study, *N*-acylurea derivatives **175** are prepared by the reaction of benzoic acid derivatives **38** with *N,N'*-disubstituted carbodiimides **174** in neat conditions (Filho, 2007).



Scheme 1.4.5 MW-assisted synthesis of *N*-acylurea derivatives

Soeta and Ukaji (2013), investigated the oxidative coupling reaction of various kind of aldehydes **176** with *N,N'*-disubstituted carbodiimides **174** catalyzed by *N*-heterocyclic carbene under aerobic conditions to furnish *N*-acyl derivatives **175** in good to high yields.



Scheme 1.4.6 *N*-heterocyclic carbene catalyzed formation of *N*-acylureas

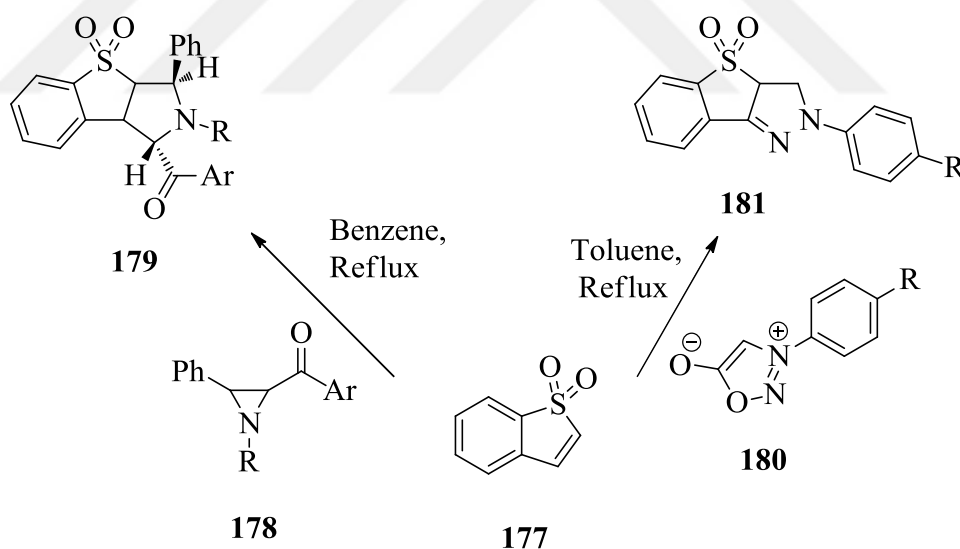
1.5 CHAPTER 5

1.5.1 Benzo[b]thiophene 1,1-dioxide, 2-nitromethylene thiazolidine and sulfone

1.5.1.1 Benzo[b]thiophene 1,1-dioxide

Benzo[b]thiophene derivatives are widely used synthetic targets and encompass a great number of biological activities such as zileuton, a potent and selective inhibitor of 5-lipoxygenase, Hsiao (1992), various cytotoxic properties, Villar, (2004) and hepatitis C virus NS5B polymerase inhibition (Chen, 2009).

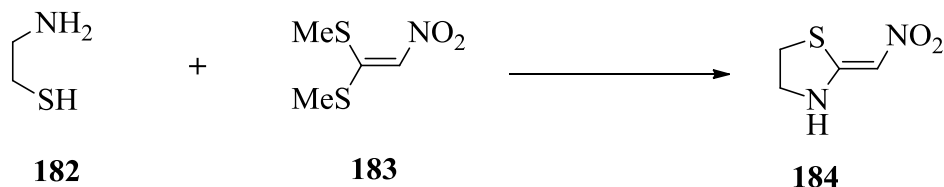
The cycloaddition reactions of benzo[b]thiophene 1,1-dioxide **177** with various kind of dipoles such as diazomethane, Fischer (1980), diphenyl nitron, Bened, (1984), nitrile imides, Sauter (1974), nitrile oxides, Bened (1982), azomethine ylides **178**, Malatesti (2006), Lakshmi (2010) and sydnone **180**, Dürüst (2014), to furnish benzo[b]thiophene derivatives **179**, **181**.



Scheme 1.5.1 1,3-dipolar cycloaddition reactions of benzo[b]thiophene 1,1-dioxide

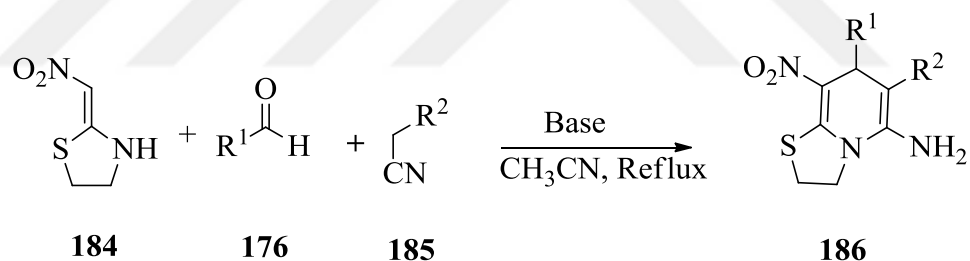
1.5.1.2 2-Nitromethylene thiazolidine

2-Nitromethylene thiazolidine **184** is a heterocyclic nitroenamine which were prepared very efficiently from the reaction of 1,1-bis(methylthio)-2-nitroethene **183** with 2-mercaptoethylamine **182** (Rajappa, 1982; Cornwall, 1998).



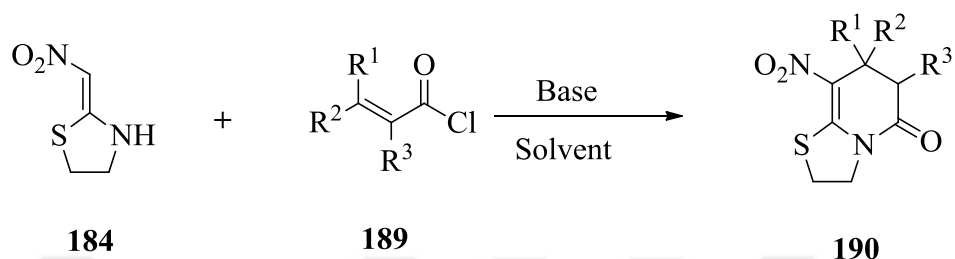
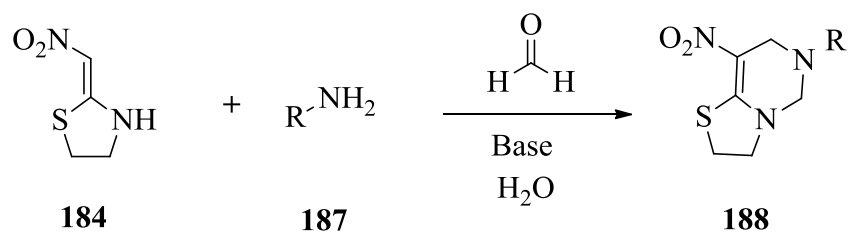
Scheme 1.5.2 Synthesis of 2-nitromethylene thiazolidine

Altug et al. (2011), demonstrated that the multicomponent reaction between 2-nitromethylenethiazolidine **184**, aromatic aldehydes **176** and nitriles **185** containing an active methylene group in the presence of base under mild conditions to furnish thiazolo[3,2-a]pyridines derivatives **186**.

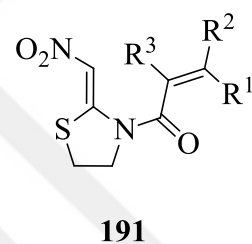


Scheme 1.5.3 Multicomponent reaction

Yildirim and co-workers, (2014a), (2014b) were reported the multicomponent cyclisation of 2-nitromethylene thiazolidine **184** with formaldehyde and various aliphatic or aromatic amines **187** in water, to give thiazolo[3,2-c]pyrimidine derivatives **188** and the reactions of 2-nitromethylene thiazolidine **184** with substituted acryloyl chlorides **189** using homogenous or heterogenous bases under mild conditions to furnish thiazolo[3,2-a] pyridinones **190**.

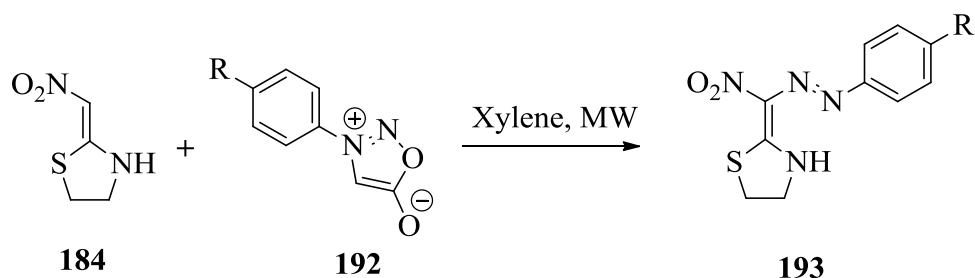


or



Scheme 1.5.4 Multicomponent cyclisation and one-pot cyclocondensation reactions of 2-nitromethylene thiazolidine

Reaction of 2-nitromethylene thiazolidine **184** with *N*-aryl sydnones **192** to give (Z)-2-(Nitro((*E*)-*p*-substitutedphenyldiazenyl)methylene)thiazolidines **193** was reported by Dürüst et al (2014).

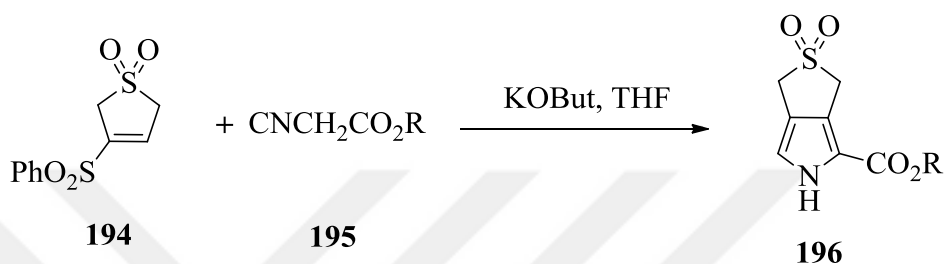


Scheme 1.5.5 Microwave-assisted coupling reaction of *N*-aryl sydnones with 2-nitromethylenethiazolidine

1.5.1.3 Sulfolene

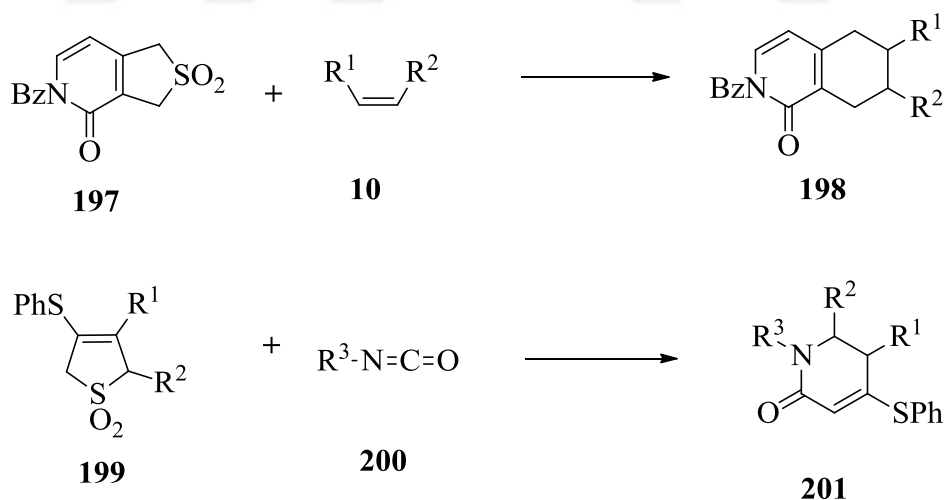
Sulfolene is highly useful as synthetic intermediate for a wide range of purposes. Sulfolene derivatives are useful dipolarophiles and precursors to 1,3-dienes with predictable double bond geometry (Leonard, 1997).

The cycloaddition reaction of sulfolene **194** with ethyl isocyanoacetate **195** to give pyrrole-fused 3-sulfolenes **196** which are valuable precursors for the synthesis of tetrabenzoporphyrins (Vicente, 1997).



Scheme 1.5.6 Cycloaddition reaction of sulfolene

There are much more diels-alder reaction of sulfolene derivatives which are precursors to 1,3-dipoles with dienophile (Chou, 2011; Govaerts, 2003; Yao, 2002).



Scheme 1.5.7 Diels-Alder reaction of sulfolenes

2. AIM AND SCOPE OF THE STUDY

There are many synthetic methodologies to generate nitrogen containing heterocycles which are an important skeletons of class the medicinal or pharmacologically and agrochemically important compounds. One important class of nitrogen containing heterocycles is pyrroles. One of the most important approaches, 1,3-dipolar cycloaddition reactions of münchnones which are *in situ* generated from *N*-acyl amino acids with alkenes are the versatile to furnish pyrrole derivatives.

All *N*-(acyl)-*N*-methylglycine **206a-k** were prepared by a two-sequence protocol. (Cantillo, 2010). Also, *N*-acetyl-*N*-benzylalanine **206l** was prepared by the alkylation of benzylamine with ethyl α -bromophenylacetate **217**, acylation with acetyl chloride and saponification (Gribble, 2013).

In first part, we examine the cycloaddition of these münchnone precursors with benzo[b]thiophene 1,1-dioxide. This provides an efficient approach to prepare fused pyrrole derivatives with accompanying deoxygenation of sulfone moiety.

Second part describes a Dakin-West type reaction between münchnone precursors, acetic anhydride and 2-nitromethylenethiazolidine. This provides a new approach to show 2-nitromethylenethiazolidine which is likely acting as a base through its enamine tautomer.

In third chapter is proposed a novel efficient route to give *N*-acylurea derivatives is described by the reaction between münchnone precursors with carbodiimides in the presence of a base. This reaction demonstrates the influence of the carbodiimides unit on both effective reagents in cyclodehydration and a reaction reagent.

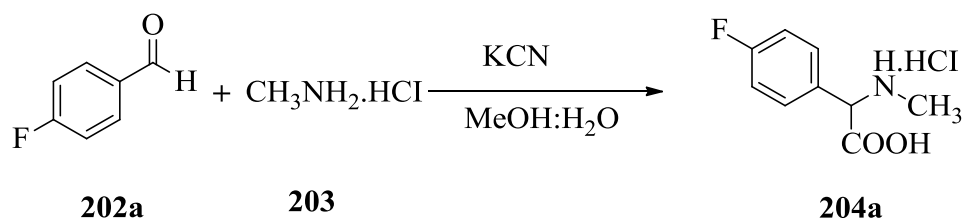
3. MATERIALS AND METHODS

Microwave reactions were carried out in the CEM DISCOVER microwave reactor. Melting points were determined on a Meltemp apparatus and are uncorrected. Infrared spectra as KBr pellet or neat were recorded on Shimadzu 8400-S spectrophotometers. Mass spectra were recorded on Waters 2695 Alliance Micromass ZQ LC/MS instrument. HRMS measurements were performed on a Waters Synapt spectrometer. NMR spectra were recorded on Jeol and Varian spectrometers operating at 400 MHz for ^1H and at 100 MHz for ^{13}C , at 25 °C. All chemical shifts are reported in ppm downfield from TMS. Coupling constants (J) are reported in Hz. Routine TLC analyses were carried out on precoated silica gel plates with fluorescent indicator. Flash column chromatography was performed on silica gel (230-400 Mesh ASTM). The stain solutions of potassium permanganate and iodine were used for visualization of the TLC spots.

3.1. Experimental

General Procedure for the preparation of C-(4-Substitutedphenyl)-N-(benzoyl)-N-methylglycine derivatives and C-(4-Substitutedphenyl)-N-(acetyl)-N-benzylglycine 1a-k.

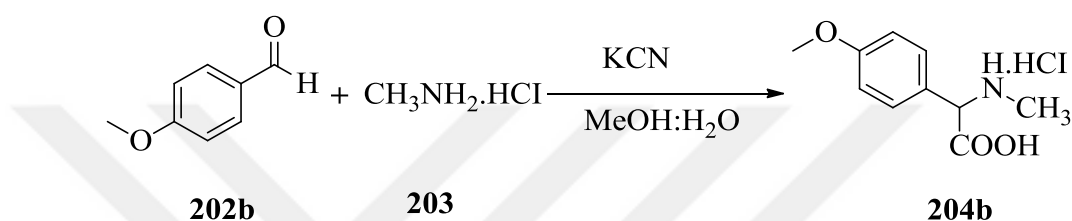
Synthesis of C-(4-fluorophenyl)-N-methylglycine hydrochloride (204a) (Cantillo, 2010; Gribble, 2013)



To a solution of 4-fluorobenzaldehyde **202a** (195.5 mmol, 24.5 g) in methanol (40 mL) was added a solution of potassium cyanide (147.0 mmol, 9.5 g) and methyl ammonium chloride **203** (222.0 mmol, 15.0 g) in water (40 mL). The mixture was stirred at room temperature for 4 h, then diluted with water (100 mL), and extracted with benzene (3x21 mL). The organic phase was extracted again with HCl 6M (3X24 mL), the aqueous layer was separated and heated at reflux for 10 h. The solution was

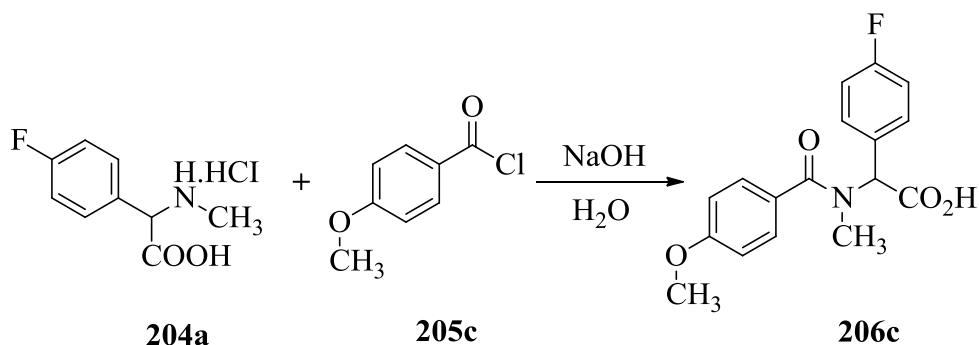
cooled to room temperature, and the resulting crystals were filtered and washed with CHCl_3 . Yellow solid. Yield: 31%. IR (KBr): $\nu = 1743, 1589, 1518, 1398, 1224, 1151, 1095, 943 \text{ cm}^{-1}$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): $\delta = 10.10$ (s, 1H), 9.76 (s, 1H), 7.57 (dd, $J=12.0$ Hz, 4.0 Hz, 2H), 7.29 (d, $J=8.0$ Hz, 2H), 5.10 (s, 1H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): $\delta = 169.5, 162.0, 131.8, 127.9, 116.7, 62.5, 31.1$. LC-MS (ES^+) m/z (%): 184 [$\text{M}^+ - \text{HCl}$].

Synthesis of C-(4-methoxyphenyl)-N-methylglycine hydrochloride (204b)
(Cantillo, 2010; Gribble, 2013)



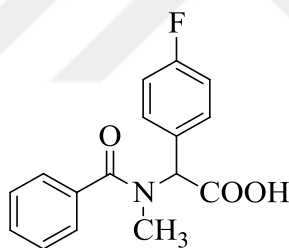
To a solution of 4-methoxybenzaldehyde **202b** (300.0 mmol, 40.85 g) in methanol (62 mL) was added a solution of potassium cyanide (225.6 mmol, 14.69 g) and methyl ammonium chloride **203** (340.7 mmol, 23.0 g) in water (62 mL). The mixture was stirred at room temperature for 4 h, then diluted with water (125 mL), and extracted with benzene (3x25 mL). The organic phase was extracted again with HCl 6M (3X30 mL), the aqueous layer was separated and heated at reflux for 10 h. The solution was cooled to room temperature, and the resulting crystals were filtered and washed with CHCl_3 . Yellow solid. Yield: 35%. IR (KBr): $\nu = 1732, 1585, 1516, 1384, 1188, 1030, 945 \text{ cm}^{-1}$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): $\delta = 14.16$ (s, 1H), 9.72 (s, 1H), 7.40 (d, $J=8.0$ Hz, 2H), 7.01 (d, $J=8.0$ Hz, 2H), 4.96 (s, 1H), 3.76 (s, 3H), 2.47 (s, 3H). LC-MS (ES^+) m/z (%): 196 [$\text{M}^+ - \text{HCl}$].

2-(4-Fluorophenyl)-2-(4-methoxy-*N*-methylbenzamido)acetic acid (**206c**)



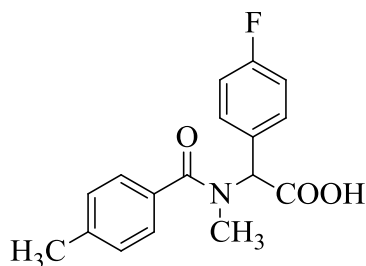
To solution of C-(4-fluorophenyl)-*N*-methylglycine hydrochloride **204a** (18.72 mmol, 4.110 g) and NaOH (55.14 mmol, 2.206 g) in water (33 mL) was added dropwise 4-methoxybenzoyl chloride **205c** (17.19 mmol, 2.932 g). The mixture was stirred for 4 h, and then HCl (12M, 4.8 mL) was added. The resulting solid was filtered off and washed with water.

2-(4-Fluorophenyl)-2-(*N*-methylbenzamido)acetic acid (**206a**)



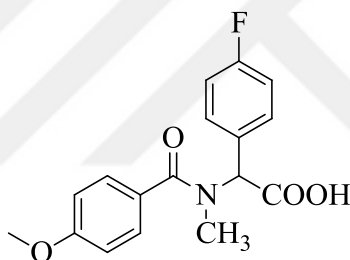
Brown oil. Yield: 62%. IR (KBr): ν = 2978, 1712, 1604, 1402, 1317, 1228, 1072, 715 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ = 13.01 (s, 1H), 7.91 (d, *J* = 8.0 Hz, 2H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.51-7.39 (m, 4H), 7.22 (t, *J* = 8.0 Hz, 3H), 6.03 (s, 1H), 2.63 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 171.7, 167.9, 163.6, 161.1, 133.4, 131.3, 129.8, 129.1, 127.5, 116.1, 26.6. LC-MS (ES⁺) *m/z* (%): 286 [M⁺-H].

2-(*N*,4-Dimethylbenzamido)-2-(4-fluorophenyl)acetic acid (206b)



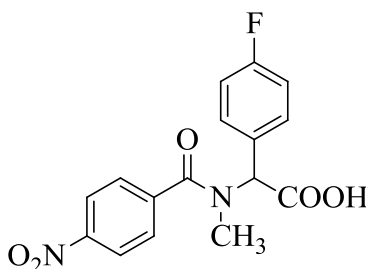
Yellow oil. Yield: 86%. IR (KBr): ν = 2924, 1735, 1608, 1512, 1396, 1230, 1072, 736 cm^{-1} . ^1H NMR (400 MHz, DMSO): δ = 13.00 (s, 1H), 7.79 (d, J =8.0 Hz, 1H), 7.38-7.20 (m, 7H), 5.99 (s, 1H), 3.28 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ = 171.7, 167.9, 160.0, 143.5, 129.9, 129.6, 128.5, 116.2, 115.9, 60.9, 20.9. LC-MS (ES^+) m/z (%): 302 [$\text{M}^+ + \text{H}$].

2-(4-Fluorophenyl)-2-(4-methoxy-*N*-methylbenzamido)acetic acid (206c)



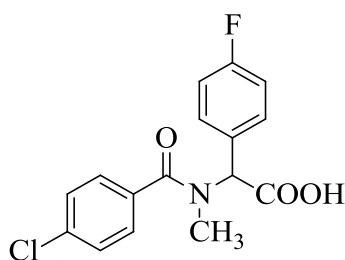
Yellow solid. Yield: 70%. M.p. 60-62 $^{\circ}\text{C}$ (lit Cantillo (2010), m.p. 57-58 $^{\circ}\text{C}$). IR (KBr): ν = 2985, 1726, 1602, 1510, 1253, 1163, 1022, 771 cm^{-1} . ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 12.81 (s, 1H), 7.85 (d, J =8.0 Hz, 3H), 7.38-7.20 (m, 4H), 6.97 (t, J =12.0 Hz, 3H), 5.93 (s, 1H), 3.78 (s, 3H), 2.68 (s, 3H). LC-MS (ES^+) m/z (%): 318 [$\text{M}^+ + \text{H}$].

2-(4-Fluorophenyl)-2-(*N*-methyl-4-nitrobenzamido)acetic acid (206d)



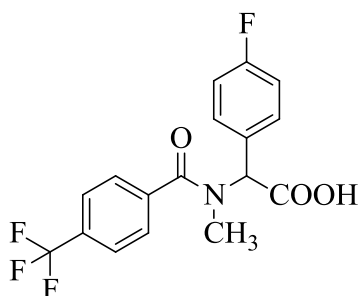
Yellow solid. Yield: 75%. M.p. 133-135 °C. IR (KBr): ν = 3113, 1697, 1635, 1512, 1350, 1226, 1072, 717 cm^{-1} . ^1H NMR (400 MHz, DMSO): δ = 13.65 (s, 1H), 8.34-8.24 (m, 4H), 8.18-8.09 (m, 4H), 6.04 (s, 1H), 2.75 (s, 3H). LC-MS (ES^+) m/z (%): 331 [$\text{M}^+ - \text{H}$].

2-(4-Chloro-*N*-methylbenzamido)-2-(4-fluorophenyl)acetic acid (206e)



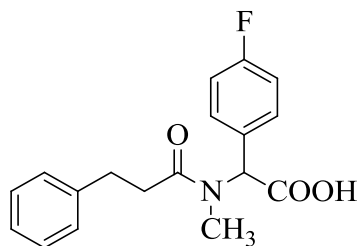
White solid. Yield: 75%. M.p. 75-77 °C. IR (KBr): ν = 3097, 1724, 1685, 1593, 1404, 1222, 1091, 759 cm^{-1} . ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 13.17 (s, 1H), 7.90 (d, J =8.0 Hz, 3H), 7.58-7.48 (m, 4H), 7.28-7.19 (m, 3H), 5.99 (s, 1H), 2.63 (s, 3H). LC-MS (ES^+) m/z (%) : 322 [$\text{M}^+ + \text{H}$].

2-(4-Fluorophenyl)-2-(*N*-methyl-4-(trifluoromethyl)benzamido)acetic acid (206f)



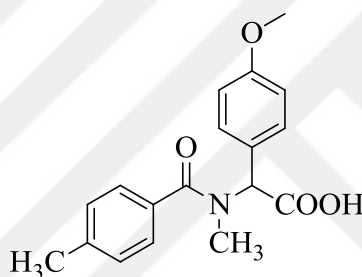
White solid. Yield: 90%. M.p. 74-76 °C. IR (KBr): ν = 2935, 1701, 1608, 1512, 1323, 1230, 1126, 860 cm^{-1} . ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 14.36 (s, 1H), 8.10 (d, J =8.0 Hz, 2H), 7.82 (dd, J =8.0 Hz, 4.0 Hz, 5H), 7.23 (t, J =8.0 Hz, 3H), 6.03 (s, 1H), 2.60 (s, 3H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ = 171.3, 166.8, 135.1, 132.9, 132.2, 130.6, 129.9, 126.1, 116.2, 116.0, 79.5, 60.8, 35.8. LC-MS (ES^+) m/z (%) : 356 [$\text{M}^+ + \text{H}$].

2-(4-Fluorophenyl)-2-(*N*-methyl-3-phenylpropanamido)acetic acid (206g)



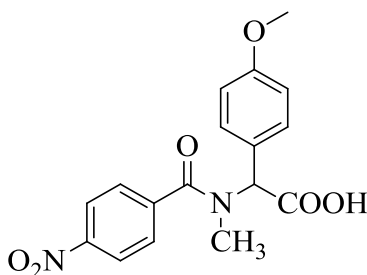
Brown oil. Yield: 65%. IR (KBr): ν = 3028, 1712, 1604, 1512, 1408, 1226, 1076, 752 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ = 9.16 (s, 1H), 7.31-7.20 (m, 9H), 5.28 (s, 1H), 2.96 (t, J =8.0 Hz, 2H), 2.69 (t, J =8.0 Hz, 2H), 2.74 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ = 177.9, 173.9, 164.5, 140.4, 131.2, 129.7, 128.5, 128.4, 126.5, 126.3, 116.0, 35.7, 32.4, 30.6. LC-MS (ES^+) m/z (%): 316 [M^+ +H].

2-(*N*,4-Dimethylbenzamido)-2-(4-methoxyphenyl)acetic acid (206h)



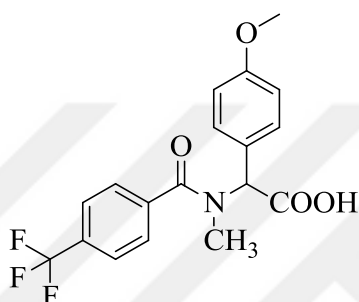
Yellow solid. Yield: 88%. M.p. 112-114°C. IR (KBr): ν = 3444, 1728, 1593, 1512, 1408, 1246, 1076, 829 cm^{-1} . ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 12.92 (s, 1H), 7.79 (d, J =8.0 Hz, 2H), 7.31-7.23 (m, 4H), 6.95 (d, J =8.0 Hz, 2H), 3.73 (s, 3H), 2.46 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ = 171.2, 167.8, 159.6, 143.6, 129.9, 129.7, 129.6, 128.5, 127.7, 126.9, 114.6, 55.7, 40.0, 21.7. LC-MS (ES^+) m/z (%) : 314 [M^+ +H].

2-(4-Methoxyphenyl)-2-(*N*-methyl-4-nitrobenzamido)acetic acid (206i)



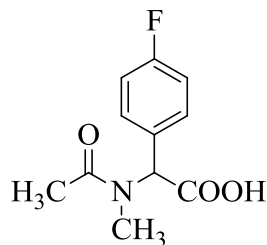
Yellow solid. Yield: 67%. M.p. 180-182 °C (lit Cantillo (2010),. m.p. 181-183°C). IR (KBr): ν = 3425, 1716, 1527, 1392, 1249, 1180, 1068, 713 cm^{-1} . ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 13.14 (s, 1H), 7.65 (d, J =8.0 Hz, 3H), 7.28 (d, J =8.0 Hz, 2H), 6.97 (d, J =8.0 Hz, 3H), 6.01 (s, 1H), 3.74 (s, 3H), 3.29 (s, 3H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ = 171.3, 169.9, 166.2, 148.3, 140.7, 131.3, 128.8, 126.6, 124.3, 114.7, 77.0, 55.1, 35.1. LC-MS (ES^+) m/z (%): 345 [$\text{M}^+ + \text{H}$].

2-(4-Methoxyphenyl)-2-(*N*-methyl-4-(trifluoromethyl)benzamido)acetic acid (206j)



Yellow solid. Yield: 90%. M.p. 122-124 °C. IR (KBr): ν = 3421, 1732, 1597, 1516, 1323, 1249, 1168, 860 cm^{-1} . ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 13.17 (s, 1H), 7.82 (dd, J =12.0 Hz, 8.0 Hz, 2H), 7.59 (d, J =8.0 Hz, 2H), 7.28 (d, J =8.0 Hz, 1H), 6.96 (d, J =8.0 Hz, 2H), 6.01 (s, 3H), 3.74 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ = 171.7, 169.9, 169.3, 131.3, 130.6, 128.1, 126.5, 126.1, 125.8, 122.9, 114.9, 60.6, 55.7, 35.1. LC-MS (ES^+) m/z (%) : 368 [$\text{M}^+ + \text{H}$].

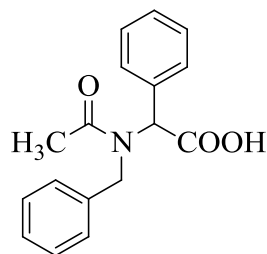
2-(4-Fluorophenyl)-2-(*N*-methylacetamido)acetic acid (206k)



White solid. Yield: 31%. M.p. 199-201 °C. IR (KBr): ν = 3471, 1743, 1608, 1516, 1392, 1222, 1030, 837 cm^{-1} . ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ = 9.93 (s, 1H), 7.57 (dd, J =8.0 Hz, 4.0 Hz, 2H), 7.29 (t, J =8.0 Hz, 2H), 5.10 (s, 1H), 2.34 (s, 3H), 2.30 (s,

3H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ = 169.6, 164.4, 161.9, 131.9, 127.9, 116.7, 62.5, 40.0, 31.1. LC-MS (ES^+) m/z (%): 225 [M^+].

2-(*N*-benzylacetamido)-2-phenylacetic acid (**206l**)



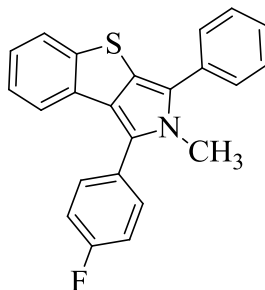
White solid. IR (KBr): ν = 3429, 1716, 1573, 1269, 1060, 964 cm^{-1} . ^1H NMR (400 MHz, DMSO): δ = 12.81 (s, 1H), 7.27-6.99 (m, 10H), 5.66 (s, 1H), 4.67 (d, J =17.8 Hz, 1H), 4.38 (d, J =17.8 Hz, 1H), 1.94 (s, 3H). LC-MS (ES^+) m/z (%): 284.0 [$\text{M}^+ + \text{H}$].

Reactions between münchnone precursors 1a-k and Benzo[b]thiophene 1,1-dioxide.

General procedure:

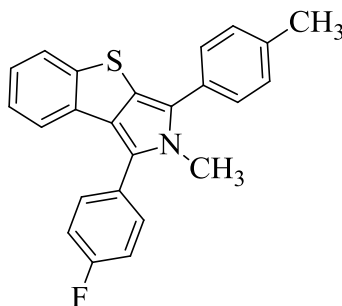
2-(4-Fluorophenyl)-2-(*N*-methyl-4-(trifluoromethyl)benzamido)acetic acid **206f** (0.500 mmol, 178 mg) was dissolved in toluene (3 mL) added acetic anhydride (0.2 mL) was irradiated at 0-150 W for 15 min in closed glass vial in a CEM microwave synthesiser at 55 °C. Then, benzo[b]thiophene 1,1-dioxide **177** (0.167 mmol, 28 mg) was added the reaction mixture and irradiated at 0-150 W for further 1.5 hour at 125 °C. After cooling the reaction mixture to room temperature, the solvent was removed under the reduced pressure and the residue was purified by silica gel flash column chromatography using ethyl acetate-*n*-hexane (1:18).

3-(4-Fluorophenyl)-2-methyl-1-phenyl-2H-benzo[4,5]thieno[2,3-c]pyrrole (207a)



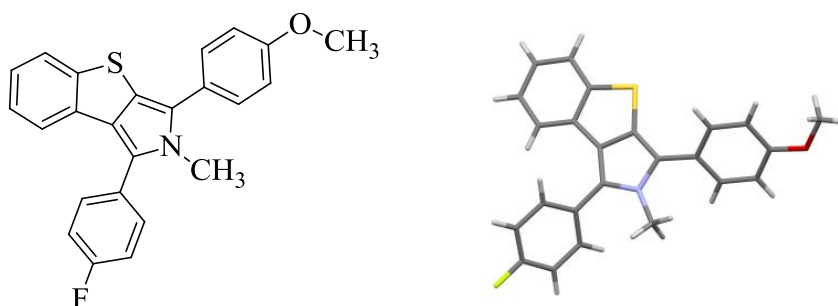
Yellow solid. Yield: 67%. M.p. 158-160 °C. IR (KBr): ν = 2831, 1562, 1502, 1342, 1174, 825, 759 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ = 7.66 (d, J = 7.6 Hz, 1H), 7.61-7.58 (m, 5H), 7.51 (dd, J = 16.4 Hz, 8.8 Hz, 3H), 7.31-7.35 (m, 1H), 7.29-7.20 (m, 2H), 7.15 (t, J = 7.6 Hz, 2H), 3.71 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ = 162.8 (d, C-F carbon, J = 261.0 Hz), 143.4, 133.1, 132.3, 132.1 (d, β -C to C-F, J_{meta} = 8.0 Hz), 131.7, 129.1, 128.9, 128.4, 128.1, 126.7, 124.7, 123.9, 123.5, 120.5, 116.0 (d, α -C to C-F, J_{ortho} = 22.0 Hz), 34.8. HRMS (ESI-TOF) m/z $[\text{M}+\text{H}]^+$ for $\text{C}_{23}\text{H}_{16}\text{FNS}$ calcd 358.1000, found 358.1036.

3-(4-Fluorophenyl)-2-methyl-1-(p-tolyl)-2H-benzo[4,5]thieno[2,3-c]pyrrole (207b)



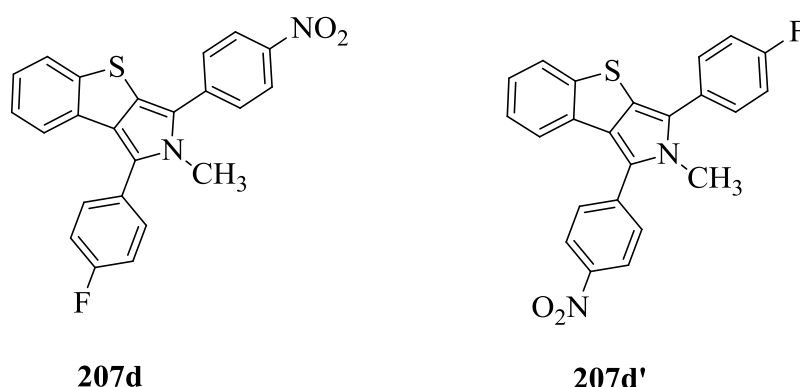
Yellow oily. Yield: 42%. IR (KBr): ν = 2926, 1514, 1508, 1340, 1155 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ = 7.64 (d, J = 7.7 Hz, 1H), 7.58 (dd, J = 8.7, 5.4 Hz, 2H), 7.52 (d, J = 7.3 Hz, 1H), 7.46 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 2.2 Hz, 1H), 7.22 (t, J = 2.3 Hz, 1H), 7.20 (s, 1H), 7.18 (d, J = 1.3 Hz, 1H), 7.13 (t, J = 8.1 Hz, 1H), 3.69 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ = 162.4 (d, C-F carbon, J = 258.0 Hz), 143.6, 136.6, 132.1 (d, β -C to C-F, J_{meta} = 8.0 Hz), 131.9, 129.7, 128.1, 126.2, 125.4, 124.7, 124.4, 124.0, 123.6, 121.1, 120.6, 116.0 (d, α -C to C-F, J_{ortho} = 22.0 Hz), 29.8, 21.4.

3-(4-Fluorophenyl)-1-(4-methoxyphenyl)-2-methyl-2H-benzo[4,5]thieno[2,3-c]pyrrole (207c)



White solid. Yield: 54%. . M.p. 197-199 °C. IR (KBr): ν = 2831, 1562, 1502, 1342, 1174, 825, 759 cm^{-1} . ¹H NMR (400 MHz, CDCl₃) δ = 7.65 (d, J = 4.0 Hz, 1H), 7.59 (dd, J = 8.8 Hz, 5.6 Hz, 2H), 7.52 (dd, J = 10.8 Hz, 8.4 Hz, 3H), 7.28-7.20 (m, 3H), 7.14 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H), 3.68 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ = 160.4 (d, C-F carbon, J = 188.0 Hz), 158.5, 143.5, 132.0 (d, β -C to C-F, J_{meta} = 8.0 Hz), 131.8, 129.6, 125.7, 124.8, 124.6, 124.0, 123.9, 123.5, 120.5, 115.9 (d, α -C to C-F, J_{ortho} = 22.0 Hz), 114.4, 55.4, 34.5. LC-MS (AP-ESI) m/z (%): 387.2 [M⁺], 404.2. HRMS (ESI-TOF) m/z [M+H]⁺ for C₂₄H₁₈FNOS calcd 388.1100, found 388.1154.

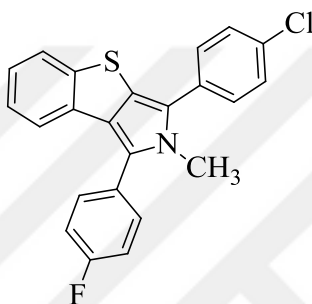
3-(4-Fluorophenyl)-2-methyl-1-(4-nitrophenyl)-2H-benzo[4,5]thieno[2,3-c]pyrrole (207d and 207d')



Red solid. Yield: 52%. M.p. 148-150 °C. IR (KBr): ν = 2928, 1502, 1473, 1336, 1155, 1095 cm^{-1} . ¹H NMR (400 MHz, CDCl₃) δ = 8.34 (d, J = 9.0 Hz, 2H), 8.16 (d, J = 8.7 Hz, 3H), 7.98 (d, J = 8.2 Hz, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 8.9 Hz, 3H), 7.68 (d, J = 9.0 Hz, 3H), 7.62 – 7.56 (m, 6H), 7.49 (dd, J = 16.2, 8.0 Hz, 3H), 7.31 –

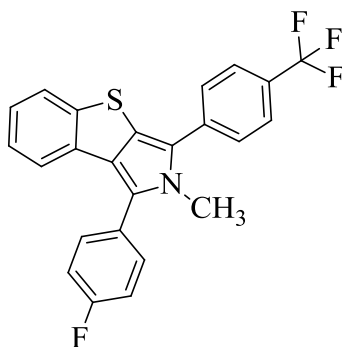
7.23 (m, 3H), 7.17 (d, $J = 8.0$ Hz, 1H), 7.00 (t, $J = 8.6$ Hz, 3H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ = 166.2 (d, C-F carbon, $J = 256.0$ Hz), 162.9 (d, C-F carbon, $J = 252.0$ Hz), 150.1, 145.2, 143.1, 142.8, 141.5, 140.6, 139.9, 138.7, 137.9, 134.5, 132.3, 132.2 (d, β -C to C-F, $J_{\text{meta}} = 8.0$ Hz), 131.9 (d, β -C to C-F, $J_{\text{meta}} = 9.0$ Hz), 131.8, 131.3, 130.0, 128.5, 127.3, 126.4, 125.4, 125.3, 124.6, 124.5, 123.7, 123.6, 122.9, 122.7, 120.8, 116.3 (d, α -C to C-F, $J_{\text{ortho}} = 17.0$ Hz), 116.1 (d, α -C to C-F, $J_{\text{ortho}} = 17.0$ Hz), 35.6, 29.8.

1-(4-Chlorophenyl)-3-(4-fluorophenyl)-2-methyl-2H-benzo[4,5]thieno[2,3-c]pyrrole (207e)



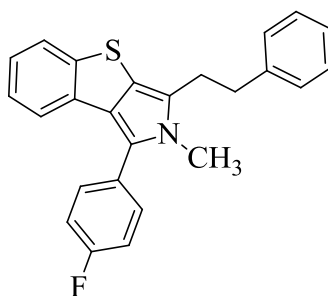
Light yellow solid. Yield: 49%. M.p. 218-220 °C. IR (KBr): ν = 3155, 1502, 1477, 1381, 1157, 1093 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ = 8.08 – 7.94 (m, 1H), 7.65 (d, $J = 8.0$ Hz, 1H), 7.59 – 7.54 (m, 2H), 7.53 – 7.41 (m, 5H), 7.29 – 7.18 (m, 4H), 7.14 (t, $J = 8.0$ Hz, 1H), 3.67 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ = 162.3 (d, C-F carbon, $J = 257.0$ Hz), 143.4, 132.5, 132.1 (d, β -C to C-F, $J_{\text{meta}} = 8.0$ Hz), 132.0, 131.9, 131.7, 130.9, 129.5, 129.3, 127.0, 126.7, 124.9, 124.2, 123.6, 120.7, 116.1 (d, α -C to C-F, $J_{\text{ortho}} = 21.0$ Hz), 34.9. HRMS (ESI-TOF) m/z $[\text{M}+\text{H}]^+$ for $\text{C}_{23}\text{H}_{15}\text{ClFNS}$ calcd 392.0676, found 392.0665.

3-(4-Fluorophenyl)-2-methyl-1-(4-(trifluoromethyl)phenyl)-2H-benzo[4,5]thieno[2,3-c]pyrrole (207f)



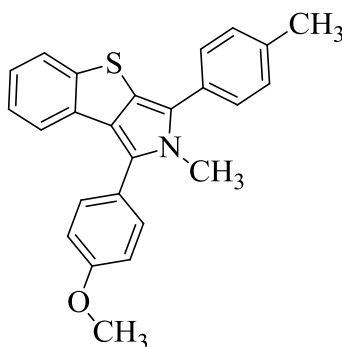
Yellow solid. Yield: 43%. M.p. 196-198 °C. IR (KBr): ν = 2922, 1508, 1329, 1159, 1074 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ = 7.74 (d, J = 8.2 Hz, 2H), 7.67 (d, J = 7.9 Hz, 2H), 7.59 (dd, J = 8.8, 5.4 Hz, 2H), 7.52 (ddd, J = 7.8, 1.3, 0.6 Hz, 1H), 7.30 – 7.21 (m, 4H), 7.16 (t, J = 7.5 Hz, 1H), 3.71 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ = 162.8 (d, C-F carbon, J = 248.0 Hz), 143.3, 135.9, 132.2 (d, β -C to C-F, J_{meta} = 8.0 Hz), 131.6, 128.0, 127.9, 127.8, 126.0 (q, C-F₃, J = 110.0 Hz), 125.9, 125.0, 124.3, 123.6, 123.1, (d, α -C to C-F₃, J = 18.0 Hz), 122.9, 120.7, 116.1 (d, α -C to C-F, J_{ortho} = 21.0 Hz), 35.1. HRMS (ESI-TOF) m/z $[\text{M}+\text{H}]^+$ for $\text{C}_{24}\text{H}_{15}\text{F}_4\text{NS}$ calcd 426.0940, found 426.0927.

3-(4-Fluorophenyl)-2-methyl-1-phenethyl-2H-benzo[4,5]thieno[2,3-c]pyrrole (207g)



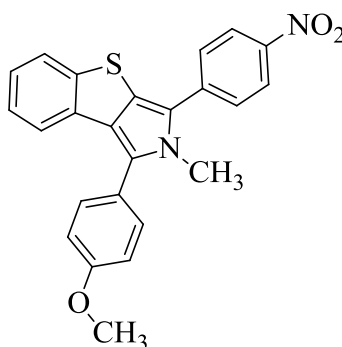
Yellow oily. Yield: 31%. IR (KBr): ν = 3155, 1506, 1465, 1386, 1157 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ = 7.74 (d, J = 7.9 Hz, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.56 – 7.49 (m, 2H), 7.47 – 7.41 (m, 2H), 7.37 (t, J = 7.9 Hz, 2H), 7.32 – 7.14 (m, 5H), 7.10 (t, J = 7.9 Hz, 1H), 3.75 (s, 3H), 3.36 (s, 2H), 3.11 (s, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ = 162.4 (d, C-F carbon, J = 256.0 Hz), 143.8, 141.3, 132.3 (d, β -C to C-F, J_{meta} = 21.0 Hz), 132.1, 128.6, 127.1, 126.4, 125.9, 124.4, 123.9, 123.5, 121.8, 120.4, 115.8 (d, α -C to C-F, J_{ortho} = 21.0 Hz), 115.7, 34.7, 32.1, 29.0.

3-(4-Methoxyphenyl)-2-methyl-1-(p-tolyl)-2H-benzo[4,5]thieno[2,3-c]pyrrole (207h)



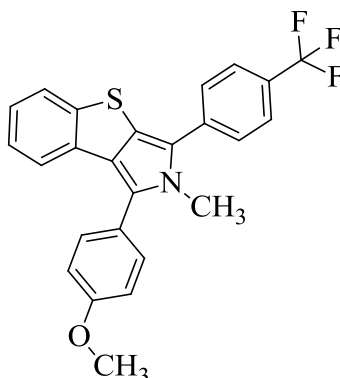
Yellow solid. Yield: 77%. M.p. 174-176°C IR (KBr): ν = 2955, 1508, 1465, 1247, 1174 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ = 7.65 (d, J = 8.1 Hz, 1H), 7.59 (dd, J = 7.8, 0.8 Hz, 2H), 7.54 (d, J = 8.7 Hz, 2H), 7.48 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 3H), 7.20 (t, J = 8.0 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.09 (d, J = 8.7 Hz, 1H), 3.91 (s, 3H), 3.70 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ = 159.4, 143.5, 136.4, 132.2, 131.7, 130.8, 129.7, 128.1, 127.4, 124.7, 124.5, 123.9, 123.8, 123.5, 120.7, 114.3, 55.5, 34.9, 21.4.

3-(4-Methoxyphenyl)-2-methyl-1-(4-nitrophenyl)-2H-benzo[4,5]thieno[2,3-c]pyrrole (207i)



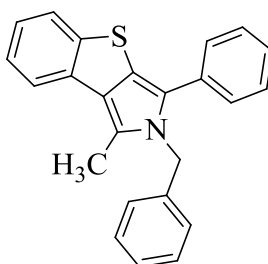
Red solid. Yield: 33%. M.p. 215-217°C IR (KBr): ν = 2928, 1506, 1471, 1336, 1174 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ = 8.33 (d, J = 8.8 Hz, 2H), 7.67 (d, J = 8.8 Hz, 3H), 7.54 (d, J = 8.7 Hz, 2H), 7.26 – 7.21 (m, 2H), 7.18 (dd, J = 7.7, 1.2 Hz, 1H), 7.11 (d, J = 8.7 Hz, 2H), 3.92 (s, 3H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ = 160.0, 144.9, 142.9, 138.9, 131.7, 131.2, 126.9, 126.1, 125.2, 125.1, 124.6, 124.5, 123.6, 122.3, 120.9, 114.5, 55.4, 29.8.

3-(4-Methoxyphenyl)-2-methyl-1-(4-(trifluoromethyl)phenyl)-2H-benzo[4,5]thieno[2,3-c]pyrrole (207j)



Yellow solid. Yield: 67%. M.p. 195-197°C IR (KBr): ν = 2958, 1508, 1458, 1325, 1172 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ = 7.72 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.3 Hz, 3H), 7.57 (d, J = 7.7 Hz, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.53 (d, J = 8.8 Hz, 2H), 7.21 (dd, J = 7.8, 1.3 Hz, 1H), 7.16 (dd, J = 7.6, 0.9 Hz, 1H), 7.09 (d, J = 8.7 Hz, 2H), 3.92 (s, 3H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ = 159.6, 143.2, 136.1, 131.8 (d, β -C to C-F_3 J = 20.0 Hz), 131.7, 129.3, 127.6, 125.8 (q, C-F_3 , J = 300.0 Hz), 125.6, 124.8, 124.2, 124.0, 123.5, 122.8 (d, α -C to C-F_3 , J = 47.0 Hz), 122.5, 120.8, 114.4, 55.5, 35.2. HRMS (ESI-TOF) m/z $[\text{M}+\text{H}]^+$ for $\text{C}_{25}\text{H}_{18}\text{FNOS}$ calcd 438.1139, found 438.1120.

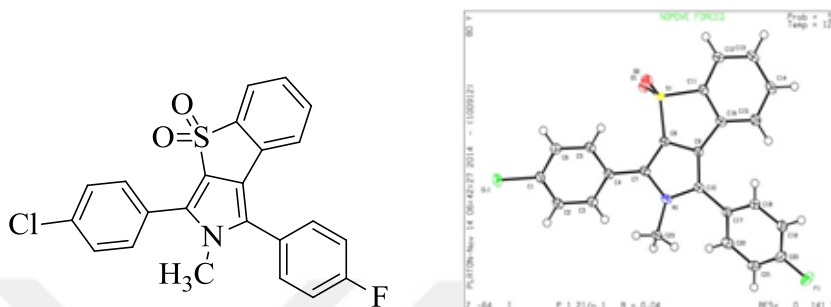
2-Benzyl-1-methyl-3-phenyl-2H-benzo[4,5]thieno[2,3-c]pyrrole (207k)



Brown oily. IR (KBr): ν = 2926, 1494, 1473, 1379, 1097 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ = 7.64 (d, J = 7.9 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.46 – 7.33 (m, 4H), 7.31 – 7.15 (m, 5H), 7.10 (t, J = 7.5 Hz, 1H), 6.90 (d, J = 7.0 Hz, 2H), 5.20 (s, 2H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ = 143.7, 138.5, 132.4, 130.3, 128.9,

128.8, 127.9, 127.3, 125.7, 125.2, 124.8, 124.5, 123.9, 123.6, 120.8, 117.9, 48.4, 12.1.

1-(4-Chlorophenyl)-3-(4-fluorophenyl)-2-methyl-2H-benzo[4,5]thieno[2,3-c]pyrrole 4,4-dioxide (208e)



m-Chloroperbenzoic acid (70-77%, 55.0 mg, 0.319 mmol) was added portionwise to a solution of **207e** (50.0 mg, 0.128 mmol) in chloroform (5 mL) at room temperature with vigorous stirring. The mixture was allowed to stir overnight at the same temperature. Then, a saturated aqueous NaHCO₃ solution (20 mL) was added and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The collected organic layers were dried, and the solvent was removed in vacuo. Crystallization from ethanol afforded white solid (46.0 mg, yield 85%).

White solid. Yield: 85%. M.p. 265-267 °C. IR (KBr): ν = 1504, 1410, 1292, 1155, 1124, 1091 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 7.67 (dd, *J* = 16.2, 7.5 Hz, 3H), 7.49 (t, *J* = 8.0 Hz, 4H), 7.32 – 7.23 (m, 5H), 7.07 (d, *J* = 8.5 Hz, 1H), 3.46 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ = 163.4 (d, C-F carbon, *J* = 249.0 Hz), 143.9, 135.5, 132.9, 132.3 (d, β -C to C-F, *J*_{meta} = 8.0 Hz), 132.2, 130.6, 129.6, 127.8, 127.4, 122.5, 121.5, 120.7, 120.0, 116.6 (d, α -C to C-F, *J*_{ortho} = 23.0 Hz), 116.5, 34.2. LC-MS (AP-ESI) *m/z* (%): 424.4 [M⁺H]. HRMS (ESI-TOF) *m/z* [M+H]⁺ for C₂₃H₁₅ClFNO₂S calcd 424.0574, found 424.0568.

Reactions between münchnone precursors (206a-k) which was used without further purification and acetic anhydride in the presence of 2-nitromethylenethiazolidine (185)

General procedure:

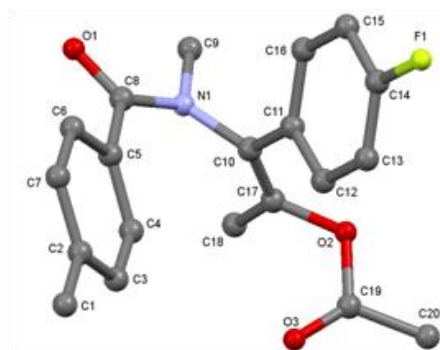
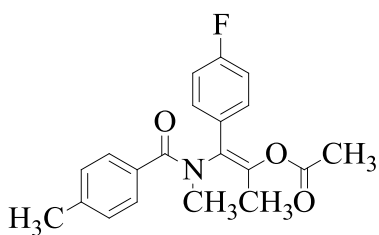
Route A:

2-(*N*,4-Dimethylbenzamido)-2-(4-fluorophenyl)acetic acid **206b** (2.80 mmol, 806 mg) was heated in acetic anhydride (8 mL) at 55°C for 30 min. Then, 2-(nitromethylene)thiazolidine **185** (1.00 mmol, 146 mg) was added to the reaction mixture and heated overnight at 90°C. After cooling the reaction to room temperature, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel, ethyl acetate-*n*-hexane mixture; 1:7) to give **5** as a yellow solid.

Route B:

2-(4-Chloro-*N*-methylbenzamido)-2-(4-fluorophenyl)acetic acid **206e** (0.715 mmol, 230 mg) in acetic anhydride (2.23 mL) was irradiated at 0-150 W for 15 min in a closed glass vial in a CEM microwave synthesiser at 55 °C. Then, 2-(nitromethylene)thiazolidine **185** (0.255 mmol, 38 mg) was added to the reaction mixture and irradiated at 0-150 W for further 45 min at 80 °C. After cooling the reaction mixture to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel flash column chromatography using ethyl acetate-*n*-hexane (1:18).

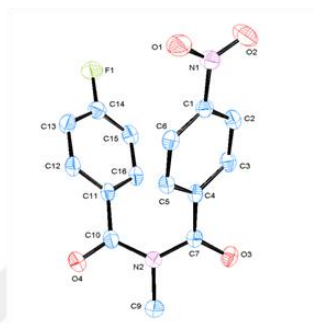
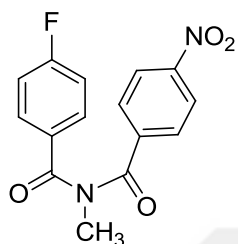
Synthesis of *E*-1-(*N*,4-dimethylbenzamido)-1-(4-fluorophenyl)prop-1-en-2-yl acetate (**209**)



Yellow solid. Yield: 48%. M.p. 98-100 °C. IR (KBr): ν = 2958, 1745, 1647, 1508, 1358, 1217, 1082, 839 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ = (7.27 (d, J =8.1 Hz, 2H), 7.13-7.10 (m, 2H), 7.01 (d, J =7.9 Hz, 2H), 6.90 (d, J =8.7 Hz, 2H), 3.31 (s, 3H), 2.30 (s, 3H), 1.98 (d, J =4.8 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ = 171.6, 168.6,

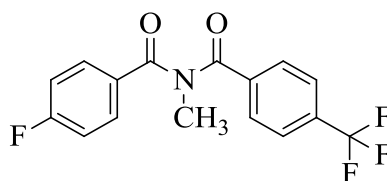
162.0 (d, C-F carbon, $J = 247.0$ Hz), 144.7, 140.4, 132.7, 132.6 (d, β -C to C-F, $J_{meta} = 18.0$ Hz), 131.1, 129.4, 129.3, 128.7, 127.5, 115.2 (d, α -C to C-F, $J_{ortho} = 22.0$ Hz), 37.2, 20.9, 17.3. LC-MS (ES^+) m/z (%): 342.2 [$M^+ + H$]. HRMS: m/z (ESI-TOF, [$M + H$]) calcd for $C_{20}H_{20}FNO_3$: 342.1505. Found: 342.1500.

4-Fluoro-*N*-methyl-*N*-(4-nitrobenzoyl)benzamide (210d) (Route A)



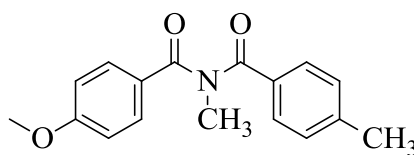
Yellow solid. Yield: 34%. M.p. 131-133 °C. IR (KBr): $\nu = 3117, 1701, 1651, 1600, 1519, 1342, 1288, 1041, 852$ cm^{-1} . ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.10$ (d, $J=8.0$ Hz, 2H), 7.62-7.56 (m, 4H), 7.00 (t, $J=8.0$ Hz, 2H), 3.50 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 173.1, 171.4, 166.3$ (d, C-F carbon, $J = 248.0$ Hz), 149.2, 141.4, 131.7 (d, β -C to C-F, $J_{meta} = 8.0$ Hz), 130.9, 129.3, 123.5, 116.2 (d, α -C to C-F, $J_{ortho} = 22.0$ Hz), 34.6. LC-MS (ES^+) m/z (%): 297 [$M-4H$]. Calculated for $C_{15}H_{11}FN_2O_4$; 302.0703; C, 59.61; H, 3.67; N, 9.27. Found: C, 59.84; H, 3.84; N, 9.22.

4-Fluoro-*N*-methyl-*N*-(4-(trifluoromethyl)benzoyl)benzamide (210f) (Route A)



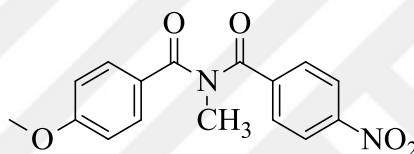
Yellow oil. Yield: 16%. IR (KBr): $\nu = 3055, 2985, 1701, 1658, 1600, 1423, 1265, 1134, 740$ cm^{-1} . ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.57$ -7.49 (m, 6H), 6.95 (t, $J=8.0$ Hz, 2H), 3.49 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 172.8, 172.8, 165.1$ (d, C-F carbon, $J = 255.0$ Hz), 139.3, 131.6 (d, β -C to C-F, $J_{meta} = 9.0$ Hz), 131.5, 130.6, 129.7, 125.5, 125.4, 116.0 (d, α -C to C-F, $J_{ortho} = 22.0$ Hz), 34.2. LC-MS (ES^+) m/z (%) : 326 [$M + H$].

4-Methoxy-N-methyl-N-(4-methylbenzoyl)benzamide (210h) (Route B)



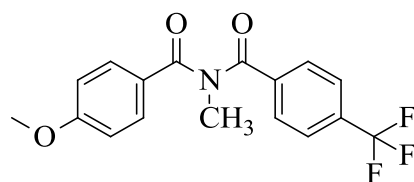
Yellow oil. Yield: 19%. IR (KBr): ν = 3055, 2985, 1685, 1647, 1604, 1512, 1265, 1172, 1045, 740 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ = 7.48 (d, J =8.0 Hz, 2H), 7.38 (d, J =8.0 Hz, 2H), 7.00 (d, J =8.0 Hz, 2H), 6.71 (dd, J =8.0 Hz 4.0 Hz, 2H), 3.74 (s, 3H), 3.46 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 174.4, 162.6, 142.5, 133.3, 132.0, 131.3, 129.2, 129.1, 128.9, 128.2, 113.7, 55.5, 34.6, 21.6. LC-MS (ES^+) m/z (%): 284 [$\text{M}+\text{H}$].

4-Methoxy-N-methyl-N-(4-nitrobenzoyl)benzamide (210i) (Route B)



Yellow oil. Yield: 21%. IR (KBr): ν = 3055, 1701, 1651, 1508, 1419, 1265, 1168, 1030 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ = 8.05 (d, J =8.0 Hz, 2H), 7.58 (d, J =8.0 Hz, 2H), 7.53 (d, J =8.0 Hz, 2H), 6.77 (d, J =8.0 Hz, 2H), 3.77 (s, 3H), 3.47 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 173.3, 171.9, 163.6, 148.9, 142.0, 131.8, 131.6, 129.2, 126.8, 123.6, 114.4, 55.7, 34.7. LC-MS (ES^+) m/z (%): 315 [$\text{M}+\text{H}$].

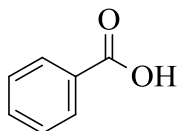
4-Methoxy-N-methyl-N-(4-(trifluoromethyl)benzoyl)benzamide (210j) (Route B)



Yellow oil. Yield: 20%. IR (KBr): ν = 3055, 1701, 1651, 1512, 1423, 1265, 1172, 1045 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ = 7.60-7.46 (m, 8H), 3.77 (s, 3H), 3.47 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 173.9, 172.8, 163.3, 139.6, 133.0, 132.1, 131.6, 128.7, 127.2, 125.3, 114.0, 55.7, 34.6. LC-MS (ES^+) m/z (%): 338 [$\text{M}+\text{H}$].

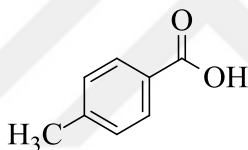
HRMS: m/z (ESI-TOF, $[M+H]^+$) calcd for $C_{17}H_{14}F_3NO_3$: 338.1004. Found: 338.1017.

Benzoic acid (211a) (Route A)



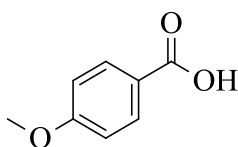
White solid. Yield: 39%. M.p. 121-123 °C (lit., Trincado (2010), Shaikh (2013), m.p. 124-126 °C). IR (KBr): ν = 3070, 1685, 1581, 1423, 1292, 1180, 1072, 705 cm^{-1} . ^1H NMR (400 MHz, $DMSO-d_6$): δ = 12.95 (s, 1H), 7.91 (d, J =8.0 Hz, 2H), 7.59 (t, J =8.0 Hz, 1H), 7.46 (t, J =8.0 Hz, 2H). ^{13}C NMR (100 MHz, $DMSO-d_6$): δ = 167.9, 131.3, 129.8, 129.4, 129.1. LC-MS (ES^-) m/z (%): 121 [M^+-H].

4-Methylbenzoic acid (211b) (Route A and Route B)



Yellow solid. Yield: 66%. M.p. 173-175 °C (lit., Trincado (2010), Shaikh (2013), m.p. 174-176 °C). IR (KBr): ν = 3070, 1678, 1612, 1419, 1284, 1180, 949, 756 cm^{-1} . ^1H NMR (400 MHz, $DMSO-d_6$): δ = 10.59 (s, 1H), 8.00 (d, J =8.0 Hz, 2H), 7.27 (d, J =8.0 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $DMSO-d_6$): δ = 172.4, 144.6, 130.4, 129.0, 126.9, 21.7. LC-MS (ES^-) m/z (%): 134 [M^+-H].

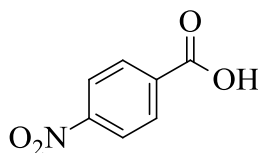
4-Methoxybenzoic acid (211c) (Route A and Route B)



White solid. Yield: 83%. M.p. 182-184 °C (lit., Trincado (2010), Shaikh (2013), m.p. 180-182 °C). IR (KBr): ν = 2985, 1685, 1604, 1516, 1261, 1165, 1026, 771 cm^{-1} . ^1H NMR (400 MHz, $DMSO-d_6$): δ = 12.59 (s, 1H), 7.95 (d, J =8.0 Hz, 2H), 6.98 (d,

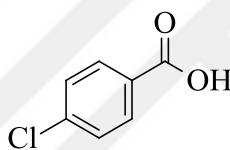
$J=8.0$ Hz, 2H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): $\delta=$ 167.6, 163.5, 131.8, 122.8, 114.2, 56.0. LC-MS (ES^-) m/z (%): 151 [M^+-H].

4-Nitrobenzoic acid (211d) (Route B)



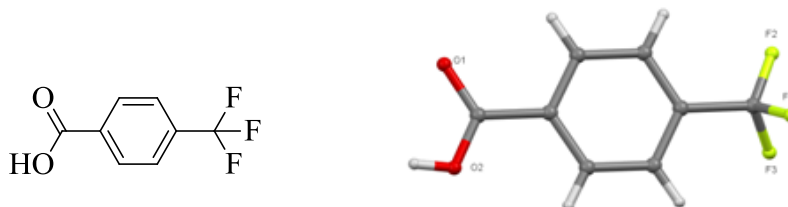
Yellow solid. Yield: 54%. M.p. 234-236 °C (lit.,Trincado (2010), Shaikh (2013), m.p. 237 °C). IR (KBr): $\nu =$ 3117, 1693, 1604, 1427, 1288, 1111, 933, 713 cm^{-1} . ^1H NMR (400 MHz, $\text{DMSO}-d_6$): $\delta=$ 13.58 (s, 1H), 8.29 (d, $J=9.1$ Hz, 2H), 8.13 (d, $J=9.1$ Hz, 2H). LC-MS (ES^-) m/z (%): 166 [$\text{M}-\text{H}$].

4-Chlorobenzoic acid (211e) (Route A and Route B)



White solid. Yield: 83%. M.p. 235-237 °C (lit.,Trincado (2010), Shaikh (2013), m.p. 236-237 °C). IR (KBr): $\nu =$ 3093, 1685, 1593, 1423, 1280, 1176, 1091, 759 cm^{-1} . ^1H NMR (400 MHz, $\text{DMSO}-d_6$): $\delta=$ 13.14 (s, 1H), 7.90 (d, $J=8.0$ Hz, 2H), 7.53 (d, $J=8.0$ Hz, 2H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): $\delta=$ 169.9, 138.3, 131.7, 130.2, 129.3. LC-MS (ES^-) m/z (%) : 155 [M^+-H].

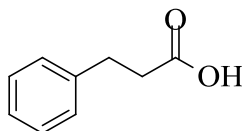
4-(Trifluoromethyl)benzoic acid (211f) (Route A and Route B)



White solid. Yield: 70%. M.p. 215-217 °C (lit.,Trincado (2010), Shaikh (2013), m.p. 219-220 °C). IR (KBr): $\nu =$ 3464, 3070, 1701, 1585, 1516, 1427, 1145, 1060, 860 cm^{-1} . ^1H NMR (400 MHz, $\text{DMSO}-d_6$): $\delta=$ 13.43 (s, 1H), 8.10 (d, $J=8.0$ Hz, 2H), 7.84

(d, $J=8.0$ Hz, 2H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): $\delta=166.7, 135.1, 133.2, 130.6, 126.1$ (q, C-F₃, $J=4.0$ Hz). LC-MS (ES^-) m/z (%): 189 [$\text{M}^+ - \text{H}$].

3-Phenylpropanoic acid (211g) (Route A)



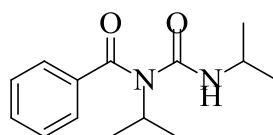
Yellow oil. Yield: 75%. IR (KBr): $\nu = 3028, 1705, 1604, 1496, 1292, 1157, 1076, 941\text{ cm}^{-1}$. ^1H NMR (400 MHz, CDCl_3): $\delta=11.67$ (s, 1H), 7.40-7.29 (m, 5H), 3.05 (t, $J=8.0$ Hz, 2H), 2.76 (t, $J=8.0$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): $\delta=179.6, 140.4, 129.8, 128.5, 126.6$. LC-MS (ES^-) m/z (%): 149 [$\text{M}^+ - \text{H}$].

Synthesis of *N*-Acylureas

General Procedure:

2-(4-chloro-*N*-methylbenzamido)-2-(4-fluorophenyl)acetic acid **206e** (0.47 mmol, 151 mg) was dissolved in acetonitrile (10 mL) and DIPC (diisopropyl carbodiimide) **163** (0.3 mL) was added. Then, the reaction mixture was heated at 55°C for 30 min. After that, DIPA (diisopropyl amine) **212** (0.2 mL) was added the reaction mixture and heated at 90 °C for overnight. After cooling the reaction to room temperature, the solvent was removed under vacuum and the residue was purified by silica gel flash column chromatography using ethyl acetate-hexane mixture (1:8).

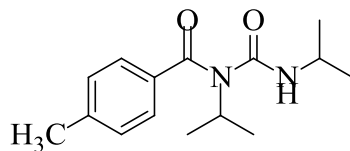
N-isopropyl-*N*-(isopropylcarbamoyl)benzamide (213a)



White solid. Yield: 45%. M.p. 112-114 °C. (lit., Soeta (2013), m.p. 114.5-115 °C) IR (KBr): $\nu = 3302, 2974, 1678, 1647, 1543, 1350, 1261, 1138, 810\text{ cm}^{-1}$. ^1H NMR (400 MHz, CDCl_3) $\delta=7.51 - 7.48$ (m, 2H), 7.46 – 7.43 (m, 1H), 7.43 – 7.39 (m, 2H), 6.69 (s, 1H), 4.39-4.34 (m, 1H), 3.85-3.76 (m, 1H), 1.41 (d, $J=6.8$ Hz, 6H), 0.96 (d, $J=$

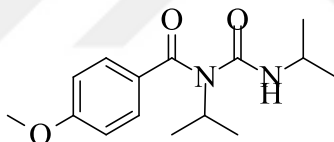
6.6 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ = 172.3, 154.1, 137.1, 130.6, 128.6, 126.3, 50.3, 42.7, 22.2, 20.8. LC-MS (ES^-) m/z (%): 249.3 [$\text{M}^+ + \text{H}$].

***N*-isopropyl-*N*-(isopropylcarbamoyl)-4-methylbenzamide (213b)**



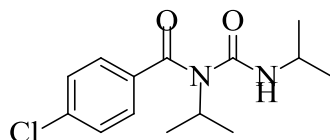
White solid. Yield: 35%. M.p. 100-102°C. IR (KBr): ν = 3329, 2974, 1701, 1635, 1512, 1257, 1130, 1057, 829 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ = 7.40 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 7.9 Hz, 2H), 6.78 (s, 1H), 4.43-4.34 (m, 1H), 3.89-3.80 (m, 1H), 2.38 (s, 3H), 1.42 (d, J = 6.8 Hz, 6H), 1.00 (d, J = 6.5 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ = 172.5, 154.3, 141.0, 134.4, 129.2, 126.5, 50.5, 42.6, 22.3, 21.4, 20.9. LC-MS (ES^-) m/z (%): 263.4 [$\text{M}^+ + \text{H}$].

***N*-isopropyl-*N*-(isopropylcarbamoyl)-4-methoxybenzamide (213c)**



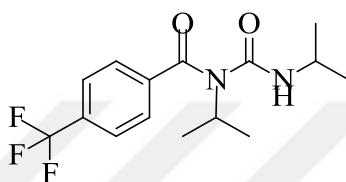
Yellow solid. Yield: 35%. M.p. 112-114 °C. IR (KBr): ν = 3336, 2931, 1693, 1600, 1516, 1346, 1257, 1084, 844 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ = 7.50 (d, J = 8.9 Hz, 2H), 6.89 (d, J = 8.9 Hz, 2H), 6.44 (s, 1H), 4.51-4.41 (m, 1H), 3.89 – 3.84 (m, 1H), 3.82 (s, 3H), 1.41 (d, J = 6.8 Hz, 6H), 0.96 (d, J = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ = 171.9, 161.7, 154.5, 129.2, 128.9, 113.8, 55.4, 50.1, 42.7, 22.3, 20.9. LC-MS (ES^-) m/z (%): 279.4 [$\text{M}^+ + \text{H}$].

***N*-isopropyl-*N*-(isopropylcarbamoyl)-4-chlorobenzamide (213d)**



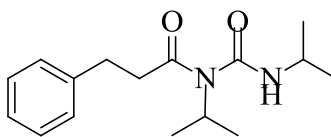
White solid. Yield: 50%. M.p. 154-156 °C. IR (KBr): $\nu = 3321, 2974, 1705, 1631, 1546, 1373, 1257, 1091, 833 \text{ cm}^{-1}$. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.46$ (d, $J=8.0$ Hz, 2H), 7.39 (d, $J=8.0$ Hz, 2H), 6.57 (s, 1H, NH), $4.42\text{--}4.34$ (m, 1H), $3.88\text{--}3.79$ (m, 1H), 1.41 (d, $J=8.0$ Hz, 6H), 0.99 (d, $J=8.0$ Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3) $\delta = 171.0, 153.8, 136.9, 135.4, 128.9, 127.9, 50.3, 42.8, 22.3, 20.9$. LC-MS (ES^-) m/z (%): $281.3 [\text{M}^+ - \text{H}]$, $326.9 [\text{M}^+ + \text{Na} + \text{CH}_3\text{CN}]$. HRMS: m/z (ESI-TOF, $[\text{M} + \text{H}]^+$) calcd for $\text{C}_{20}\text{H}_{20}\text{FNO}_3$: 342.1505. Found: 342.1500.

***N*-isopropyl-*N*-(isopropylcarbamoyl)-4-(trifluoromethyl)benzamide (213e)**



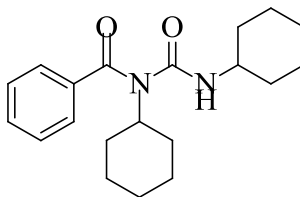
Yellow Oily. Yield: 34%. IR (KBr): $\nu = 3309, 2974, 1701, 1624, 1516, 1323, 1265, 1068, 856 \text{ cm}^{-1}$. ^1H NMR (400 MHz, CDCl_3) $\delta = 7.68$ (d, $J = 8.2$ Hz, 2H), 7.61 (d, $J = 8.2$ Hz, 2H), 6.74 (s, 1H), $4.42 - 4.15$ (m, 1H), $3.91 - 3.79$ (m, 1H), 1.42 (d, $J = 6.8$ Hz, 6H), 0.99 (d, $J = 6.6$ Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3) $\delta = 170.8, 156.6, 140.5, 127.6, 126.6, 125.7$ (q, C- F_3 , $J = 4.0$ Hz), $116.5, 50.4, 44.8, 23.6, 21.4$. LC-MS (ES^-) m/z (%): $316 [\text{M}^+]$.

***N*-isopropyl-*N*-(isopropylcarbamoyl)-3-phenylpropanamide (213f):**



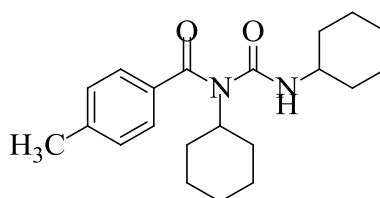
Yellow solid. Yield: 80%. M.p. 120-122 °C. (lit., Soeta (2013), m.p. 123.3-123.8 °C). IR (KBr): $\nu = 3309, 2974, 1708, 1643, 1535, 1392, 1238, 1057, 810 \text{ cm}^{-1}$. ^1H NMR (400 MHz, CDCl_3) $\delta = 7.30$ (t, $J = 7.2$ Hz, 2H), 7.22 (t, $J = 8.0$ Hz, 3H), $4.34\text{--}4.27$ (m, 1H), $3.97\text{--}3.89$ (m, 1H), 2.98 (t, $J = 7.6$ Hz, 2H), 2.73 (t, $J = 7.6$ Hz, 2H), 1.35 (d, $J = 6.8$ Hz, 6H), 1.15 (d, $J = 6.6$ Hz, 6H). ^{13}C NMR (100MHz, CDCl_3) $\delta = 173.6, 153.8, 140.7, 128.6, 128.5, 126.4, 48.1, 42.6, 37.9, 31.5, 22.5, 20.9$. LC-MS (ES^-) m/z (%): $277.5 [\text{M}^+ + \text{H}]$.

***N*-cyclohexyl-*N*-(cyclohexylcarbamoyl)benzamide (214a):**



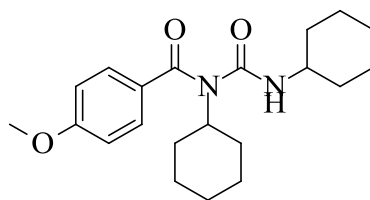
White solid. Yield: 67%. M.p. 171-173 °C. (lit., Soeta (2013), m.p. 173.5-174.0 °C). IR (KBr): $\nu = 3271, 2931, 1701, 1624, 1539, 1377, 1234, 1084, 895 \text{ cm}^{-1}$. ^1H NMR (400 MHz, CDCl_3) $\delta = 7.51$ (d, $J = 6.9 \text{ Hz}$, 2H), 7.44 (t, $J = 7.3 \text{ Hz}$, 1H), 7.37 (t, $J = 7.5 \text{ Hz}$, 2H), 6.16 (s, 1H), 4.10-4.04 (m, 1H), 3.63 – 3.29 (m, 1H), 2.08 – 1.97 (m, 3H), 1.79 (t, $J = 12.2 \text{ Hz}$, 4H), 1.55 (t, $J = 16.0 \text{ Hz}$, 5H), 1.21 (t, $J = 8.0 \text{ Hz}$, 5H), 1.10 – 1.02 (m, 1H), 0.84 (dd, $J = 21.3, 9.8 \text{ Hz}$, 2H). ^{13}C NMR (100 MHz, CDCl_3) $\delta = 171.3, 154.3, 137.0, 130.7, 128.5, 126.6, 125.5, 57.4, 49.6, 32.2, 30.7, 26.2, 25.2, 24.5$. LC-MS (ES^-) m/z (%): 329.6 [$\text{M}^+ + \text{H}$].

***N*-cyclohexyl-*N*-(cyclohexylcarbamoyl)-4-methylbenzamide (214b)**



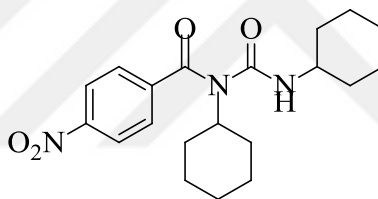
White solid. Yield: 40%. M.p. 150-152 °C. (lit., Soeta (2013), m.p. 152.0-152.0 °C). IR (KBr): $\nu = 3309, 2928, 1701, 1647, 1534, 1342, 1234, 1080, 829 \text{ cm}^{-1}$. ^1H NMR (400 MHz, CDCl_3) $\delta = 7.43$ (d, $J = 8.0 \text{ Hz}$, 2H), 7.19 (d, $J = 8.1 \text{ Hz}$, 2H), 6.24 (s, 1H), 4.09-4.02 (m, 1H), 3.50 (d, $J = 8.3 \text{ Hz}$, 1H), 2.38 (s, 3H), 2.06 (dd, $J = 24.6, 12.4 \text{ Hz}$, 2H), 1.79 (t, $J = 12.0 \text{ Hz}$, 3H), 1.66 – 1.51 (m, 6H), 1.34 – 1.05 (m, 7H), 0.91 (dd, $J = 19.8, 8.4 \text{ Hz}$, 2H). ^{13}C NMR (100 MHz, CDCl_3) $\delta = 171.9, 154.6, 141.2, 133.9, 129.2, 126.7, 57.7, 49.4, 32.3, 30.7, 26.2, 25.4, 25.2, 24.5, 21.5$. LC-MS (ES^-) m/z (%) : 343.6 [$\text{M}^+ + \text{H}$].

***N*-cyclohexyl-*N*-(cyclohexylcarbamoyl)-4-methoxybenzamide (214c)**



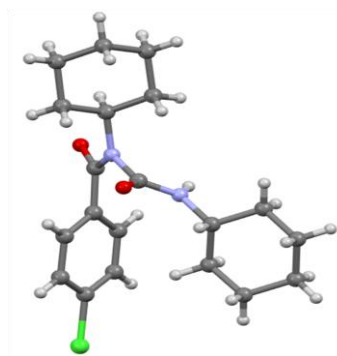
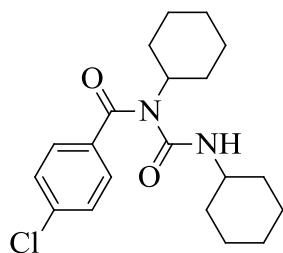
White solid. Yield: 85%. M.p. 153-155 °C. (lit., Soeta (2013), m.p. 155.0-155.5 °C). IR (KBr): $\nu = 3317, 2928, 1697, 1647, 1543, 1342, 1249, 1041, 833 \text{ cm}^{-1}$. ^1H NMR (400 MHz, CDCl_3) $\delta = 7.54$ (d, $J = 8.9 \text{ Hz}$, 2H), 6.88 (d, $J = 8.8 \text{ Hz}$, 2H), 6.03 (d, $J = 7.7 \text{ Hz}$, 1H), $4.17 - 4.06$ (m, 1H), 3.83 (s, 3H), $3.54 - 3.48$ (m, 1H), $2.07-1.98$ (m, 2H), 1.79 (t, $J = 11.7 \text{ Hz}$, 3H), $1.67 - 1.45$ (m, 6H), $1.32 - 1.01$ (m, 6H), $0.95 - 0.82$ (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) $\delta = 171.1, 161.8, 154.7, 131.3, 129.1, 113.8, 57.6, 55.4, 55.4, 49.6, 32.4, 30.9, 26.3, 25.4, 24.5$. LC-MS (ES^-) m/z (%): 359.6 [$\text{M}^+ + \text{H}$].

***N*-cyclohexyl-*N*-(cyclohexylcarbamoyl)-4-nitrobenzamide (214d)**



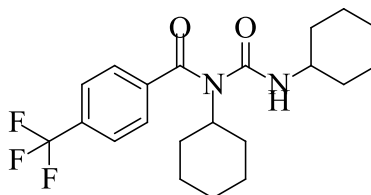
White solid. Yield: 68%. M.p. 174-176 °C. (lit., Soeta (2013), m.p. 175 °C). IR (KBr): $\nu = 3298, 2931, 1701, 1651, 1527, 1342, 1234, 1041, 856 \text{ cm}^{-1}$. ^1H NMR (400 MHz, CDCl_3) $\delta = 8.26$ (d, $J = 8.4 \text{ Hz}$, 2H), 7.70 (d, $J = 8.4 \text{ Hz}$, 2H), 6.10 (s, 1H), $4.13 - 3.90$ (m, 1H), $3.63 - 3.44$ (m, 1H), $2.04 - 1.90$ (m, 2H), $1.88 - 1.76$ (m, 4H), 1.59 (dd, $J = 20.2, 8.3 \text{ Hz}$, 6H), $1.33 - 1.05$ (m, 6H), 0.92 (dd, $J = 21.3, 10.4 \text{ Hz}$, 2H). ^{13}C NMR (100 MHz, CDCl_3) $\delta = 168.8, 153.4, 148.8, 142.7, 127.6, 123.8, 57.5, 49.8, 32.3, 30.8, 26.1, 25.2, 25.1, 24.5$. LC-MS (ES^-) m/z (%): 374.6 [$\text{M}^+ + \text{H}$].

***N*-cyclohexyl-*N*-(cyclohexylcarbamoyl)-4-chlorobenzamide (214e)**



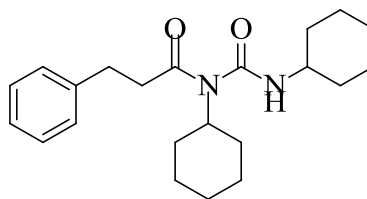
White solid. Yield: 75%. M.p. 181-183 °C. (lit., Soeta (2013), m.p. 183.1-183.3 °C). IR (KBr): $\nu = 3306, 2931, 1701, 1647, 1543, 1342, 1234, 1087, 833 \text{ cm}^{-1}$. ^1H NMR (400 MHz, CDCl_3) $\delta = 7.49$ (d, $J = 8.4 \text{ Hz}$, 2H), 7.37 (d, $J = 8.4 \text{ Hz}$, 2H), 6.06 (s, 1H), 4.10 - 4.02 (m, 1H), 3.55 – 3.49 (m, 1H), 2.09 – 1.93 (m, 2H), 1.85 – 1.71 (m, 4H), 1.67 – 1.48 (m, 5H), 1.33 – 1.04 (m, 7H), 0.98 – 0.84 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) $\delta = 169.9, 153.9, 135.27, 131.3, 130.0, 128.77, 128.7, 127.1, 115.6, 57.5, 49.7, 32.3, 30.8, 25.3, 24.5$. LC-MS (ES^-) m/z (%): $363.6 [\text{M}^+ + \text{H}]$.

***N*-cyclohexyl-*N*-(cyclohexylcarbamoyl)-4-(trifluoromethyl)benzamide (214f)**



White solid. Yield: 80%. M.p. 183-185 °C. (lit., Soeta (2013), m.p. 185.3-185.5 °C). IR (KBr): $\nu = 3309, 2935, 1701, 1651, 1543, 1327, 1130, 1064, 852 \text{ cm}^{-1}$. ^1H NMR (400 MHz, CDCl_3) $\delta = 7.66$ (dd, $J = 18.0, 4.0 \text{ Hz}$, 4H), 6.07 (s, 1H), 4.08 - 4.00 (m, 1H), 3.50 - 3.45 (m, 1H), 2.00 (q, $J = 12.4 \text{ Hz}$, 2H), 1.81 (t, $J = 11.7 \text{ Hz}$, 4H), 1.65 – 1.50 (m, 5H), 1.34 – 1.03 (m, 7H), 0.88 (dd, $J = 23.1, 11.0 \text{ Hz}$, 2H). ^{13}C NMR (101 MHz, CDCl_3) $\delta = 169.7, 153.7, 140.3, 132.5, 126.9, 125.8$ (q, C- F_3 , $J = 4.0 \text{ Hz}$), $121.8, 57.5, 49.7, 32.2, 30.7, 26.1, 25.3, 25.1, 24.4$. LC-MS (ES^-) m/z (%) : $397.5 [\text{M}^+ + \text{H}]$.

***N*-cyclohexyl-*N*-(cyclohexylcarbamoyl)-3-phenylpropanamide (214g)**



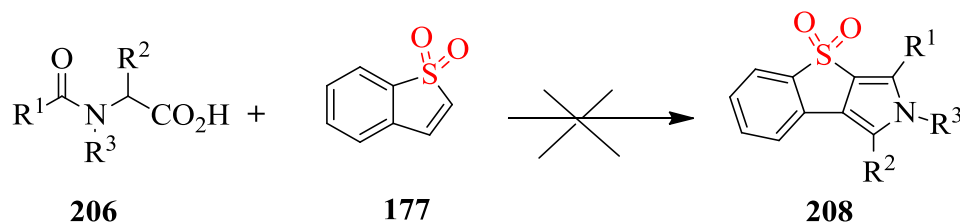
Yellow solid. Yield: 82%. M.p. 119-121 °C. (lit., Soeta (2013), m.p. 183.1-183.3 °C). IR (KBr): $\nu = 3267, 2928, 1701, 1654, 1543, 1381, 1226, 1138, 976 \text{ cm}^{-1}$. ^1H NMR (400 MHz, CDCl_3) $\delta = 7.32 - 7.23$ (m, 2H), 7.19 (dd, $J = 10.0, 7.1 \text{ Hz}$, 3H), 6.52 (s, 1H), 3.93-3.4 (m, 1H), 3.70 – 3.52 (m, 1H), 2.96 (t, $J = 7.6 \text{ Hz}$, 2H), 2.67 (t, $J = 7.6 \text{ Hz}$, 2H), 1.87 (dd, $J = 12.2, 3.2 \text{ Hz}$, 2H), 1.77-1.58 (m, 8H), 1.60 (dd, $J = 12.0, 8.0 \text{ Hz}$, 2H), 1.37-1.19 (m, 5H), 1.16-1.06 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3) $\delta = 172.4, 153.9, 140.9, 128.7, 128.6, 126.5, 126.3, 55.7, 49.9, 37.5, 32.7, 31.8, 30.9, 26.3, 25.4, 24.8$. LC-MS (ES^-) m/z (%): 357.7 [$\text{M}^+ + \text{H}$].

4. RESULTS AND DISCUSSIONS

Part 1: Synthesis of fused pyrrole derivatives

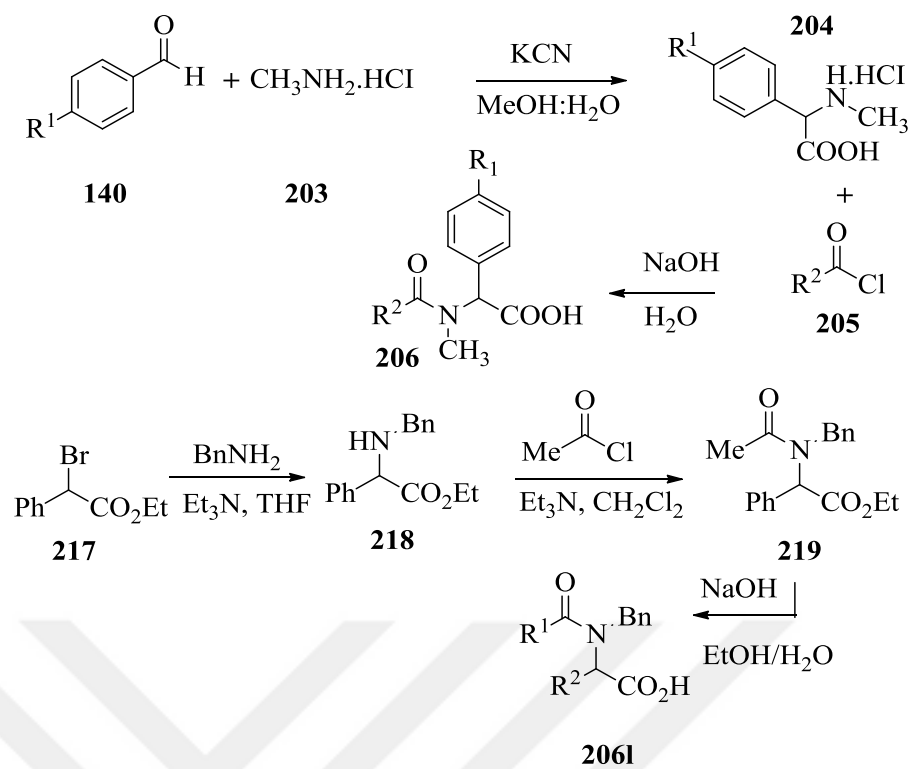
Pyrrole derivatives are important heterocycles, widely present in natural and many pharmaceutical compounds. There are many synthetic methods to prepare pyrrole derivatives in the literature. Among them, 1,3-dipolar cycloaddition reaction of münchnones with alkynes and alkenes are the versatile methods (Gribble, 1998). Also, benzo[*b*]thiophene derivatives are widely used as synthetic targets and encompass a great number of biological activities (Connor, 1992). In this respect, we have been focused on the 1,3-dipolar cycloaddition reaction of münchnones, which are *in situ* generated from the corresponding *C*-(4-substitutedphenyl)-*N*-(benzoyl)-*N*-methylglycine **206** and they were reacted with benzo[*b*]thiophene 1,1-dioxide **177** to

obtain expected cycloadducts. But, we were unsuccessful to give the expected cycloadducts after trying different solvents and reaction conditions.



Scheme 4.1 Synthesis of fused pyrrole derivatives

All *N*-(acyl)-*N*-methylglycine **206a-k** were prepared by a two-sequence protocol. The first is a multicomponent reaction of *p*-substituted benzaldehyde in methanol with potassium cyanide and methyl ammonium chloride in water to give aminonitrile. Then, this mixture was hydrolyzed with HCl to obtain the corresponding *C*-aryl-*N*-methylglycine hydrochlorides. After that, *N*-acylation of *C*-aryl-*N*-methylglycine hydrochlorides with 4-substitutedbenzoyl chlorides and acyl chloride gave rise to *N*-acyl-*N*-methylglycine derivatives which were used without further purification (Cantillo, 2010). Also, *N*-acetyl-*N*-benzylalanine **206l** was prepared by the alkylation of benzylamine with ethyl α -bromophenylacetate **217**, acylation with acetyl chloride and saponification (Gribble, 2013).



entry	substrate	R ¹	R ²	Yield %
1	206a	F	C ₆ H ₅	62
2	206b	F	p-CH ₃ -C ₆ H ₄	86
3	206c	F	p-CH ₃ O-C ₆ H ₄	70
4	206d	F	p-NO ₂ -C ₆ H ₄	75
5	206e	F	p-Cl-C ₆ H ₄	75
6	206f	F	p-CF ₃ -C ₆ H ₄	90
7	206g	F	C ₆ H ₅ -CH ₂ CH ₂	65
8	206h	F	CH ₃	31
9	206i	OCH ₃	p-CH ₃ -C ₆ H ₄	88
10	206j	OCH ₃	p-NO ₂ -C ₆ H ₄	67
11	206k	OCH ₃	p-CF ₃ -C ₆ H ₄	90
12	206l	CH ₃	C ₆ H ₅	80

Scheme 4.2 Synthesis of *N*-acyl amino acids

The münchnones were not isolated, but generated in situ by cyclodehydration of the *N*-acylamino acids which were used without purification with acetic anhydride, *N,N'*-diisopropylcarbodiimide and *N,N'*-dicyclohexylcarbodiimide as the dehydrating agents.

1,3-Dipolar cycloaddition reaction of münchnones, generated from *N*-acyl amino acids **206** *in situ*, with benzo[*b*]thiophene 1,1-dioxide **177** in toluene under microwave irradiation for 1.5 h afforded unexpected pyrrole derivatives **207**. Upon an initial examination of the structures of the reaction products, basically, on the basis of IR, NMR, LC-MS and HRMS data, despite the expected benzo[4,5]thieno[2,3-*c*]pyrrole 4,4-dioxide structures. ^1H and ^{13}C NMR spectra exactly coincide with the molecular formulas of the structures. But, LC-MS and HRMS spectra did not give molecular ion peaks. After recrystallization of compound **207c** from suitable solvent gave fine crystals and structure of cycloadduct were determined by X-Ray crystallography.

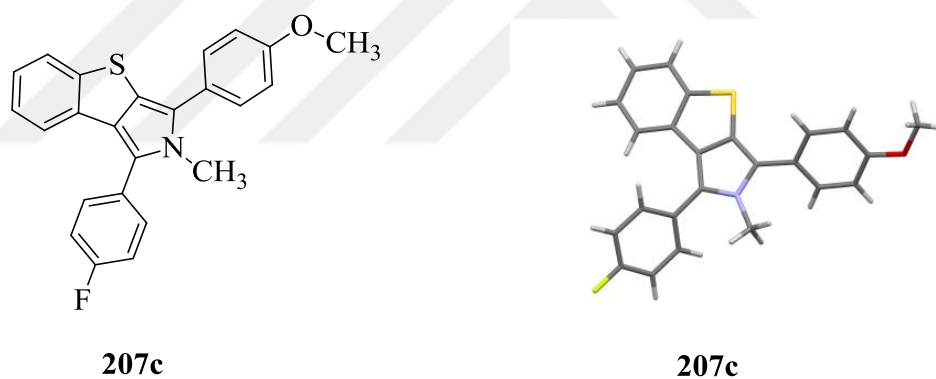
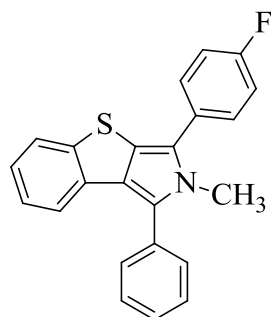


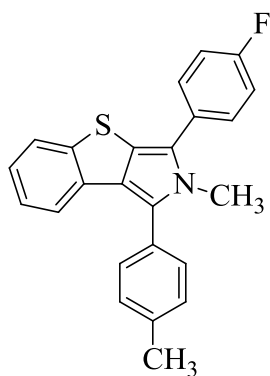
Figure 4.1 X-Ray ORTEP view of **207c**

In the IR spectra of these cycloadducts did not appeared the symmetric and asymmetric stretching vibrations of SO_2 moiety at around 1150 and 1300 cm^{-1} , respectively. Also, LC-MS spectra and HRMS measurements reveal that $[\text{M} + \text{H}]^+$ values exactly coincide with the molecular formulas of the structures.



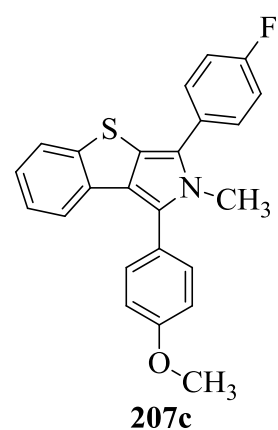
207a

Yield 67%



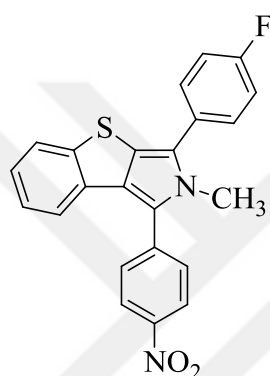
207b

Yield 42%



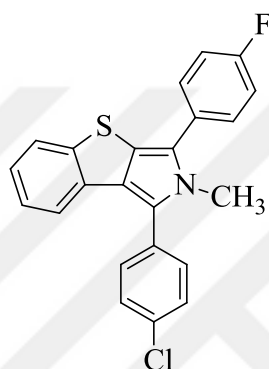
207c

Yield 54%



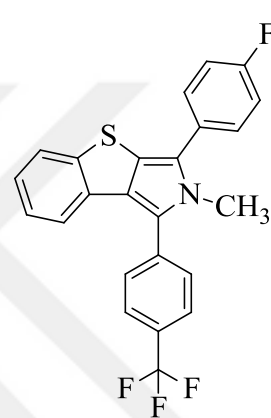
207d

Yield 51%



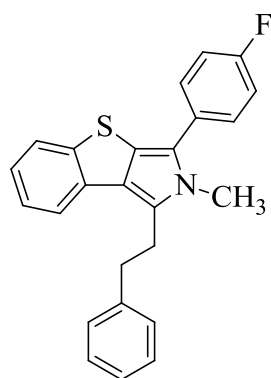
207e

Yield 49%



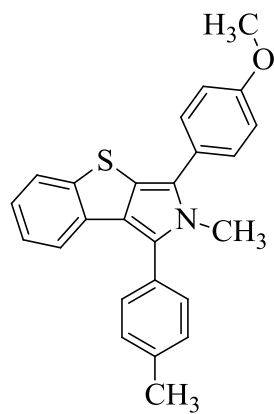
207f

Yield 43%



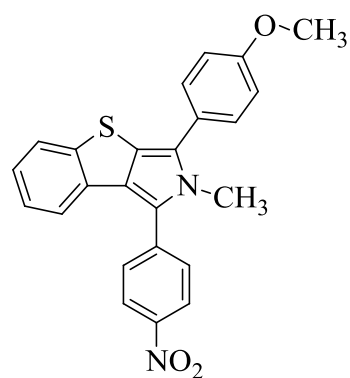
207g

Yield 31%



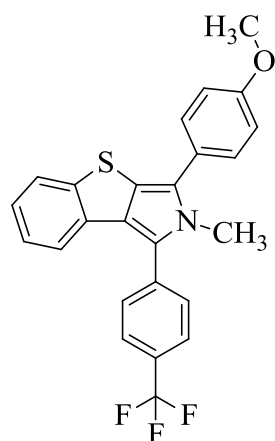
207h

Yield 77%



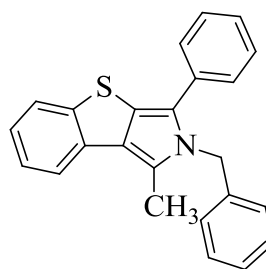
207i

Yield 33%



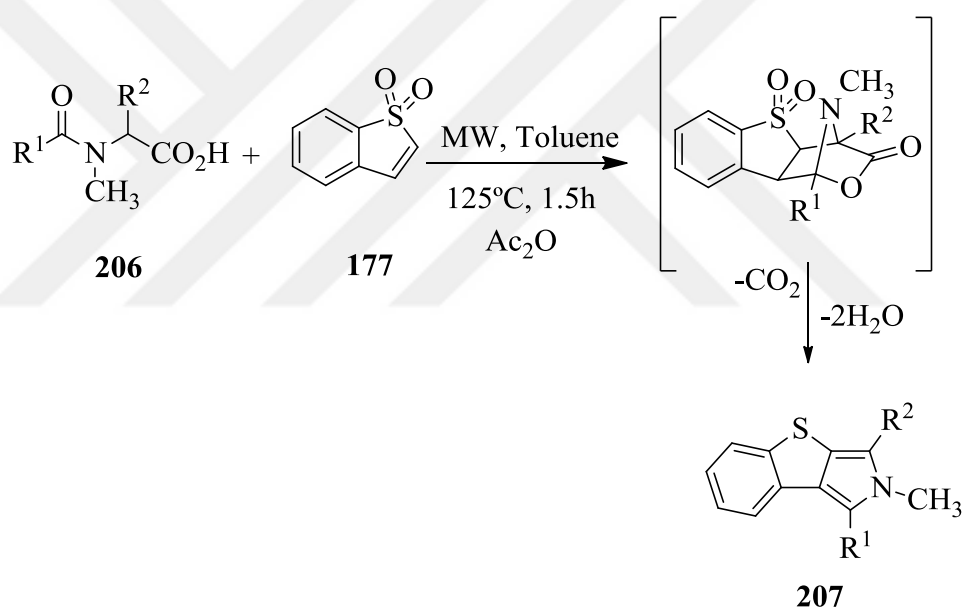
207j

Yield 67%



207k

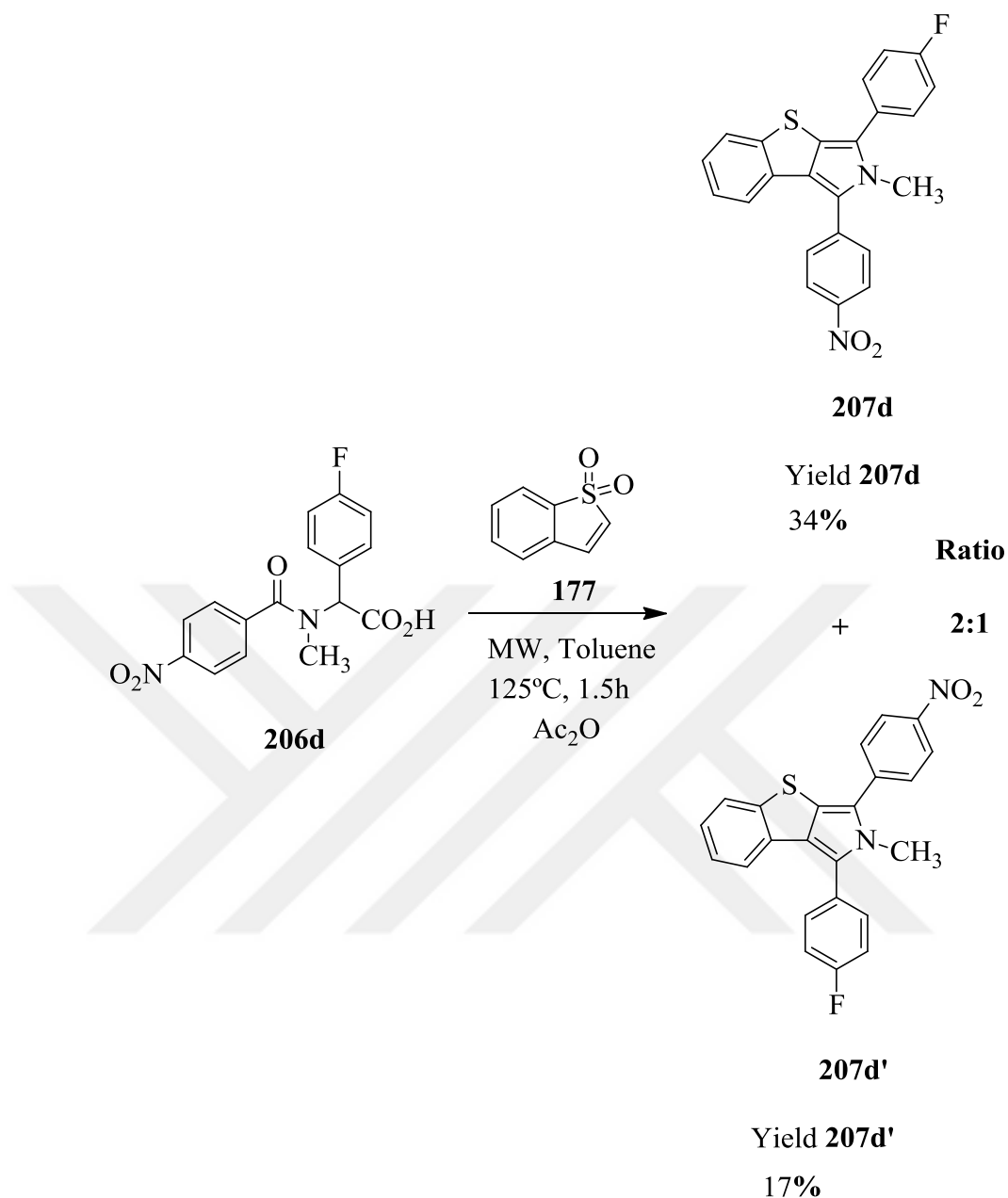
Yield 46%



^aIsolated Yields. ^bConditions: **206** (0.500 mmol), **177** (0.167 mmol), Ac₂O (0.2 mL), Toluene (3 mL), MW, 125 °C, 1.5h.

Scheme 4.3 Cycloadditions of Münchnones **206** to benzo[*b*]thiophene 1,1-dioxide **177** affording **207**^{a,b}

But, the regioisomeric mixture of NO₂-substituted pyrrole **207d** and **207d'** was obtained in 2:1 ratio which was determined by ¹H NMR peak integrations of Me groups after chromatography.



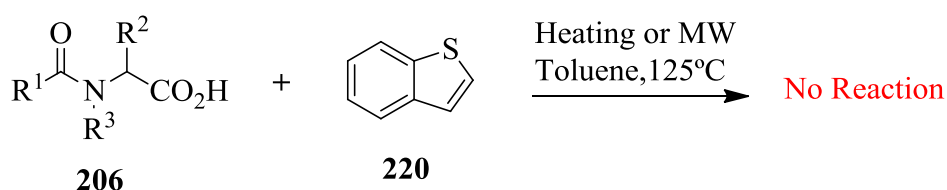
Scheme 4.4 Cycloadditions of Münchnone **206d** to benzo[*b*]thiophene 1,1-dioxide **177** affording regioisomers **207d** and **207d'**

Different type of reactions have been tried for the optimization of the reaction conditions, the best yields and results were achieved by using acetic anhydride at 125°C in toluene under microwave irradiation (Table 4.1).

Entry	Reagent	Conditions	Product
1	Ac ₂ O	Benzene reflux, 12h	No Reaction
2	DIPC	THF, reflux overnight	No Reaction
3	DCC	THF, reflux overnight	No Reaction
4	DCC	Dioxane, MW 100°C, 1h	No Reaction
5	DCC	Dioxane, reflux overnight	No Reaction
6	DCC	CH ₂ Cl ₂ rt, 2days	No Reaction
7	DCC	Toluene, reflux overnight	No Reaction
8	DIPC	Toluene, reflux overnight	No Reaction
9	Ac ₂ O	Toluene, reflux overnight	207a, 34 %
10	Ac ₂ O	Toluene, MW 125°C, 1.5h	207a, 67 %

Table 4.1 Optimization of reaction conditions to yield compound **207a**

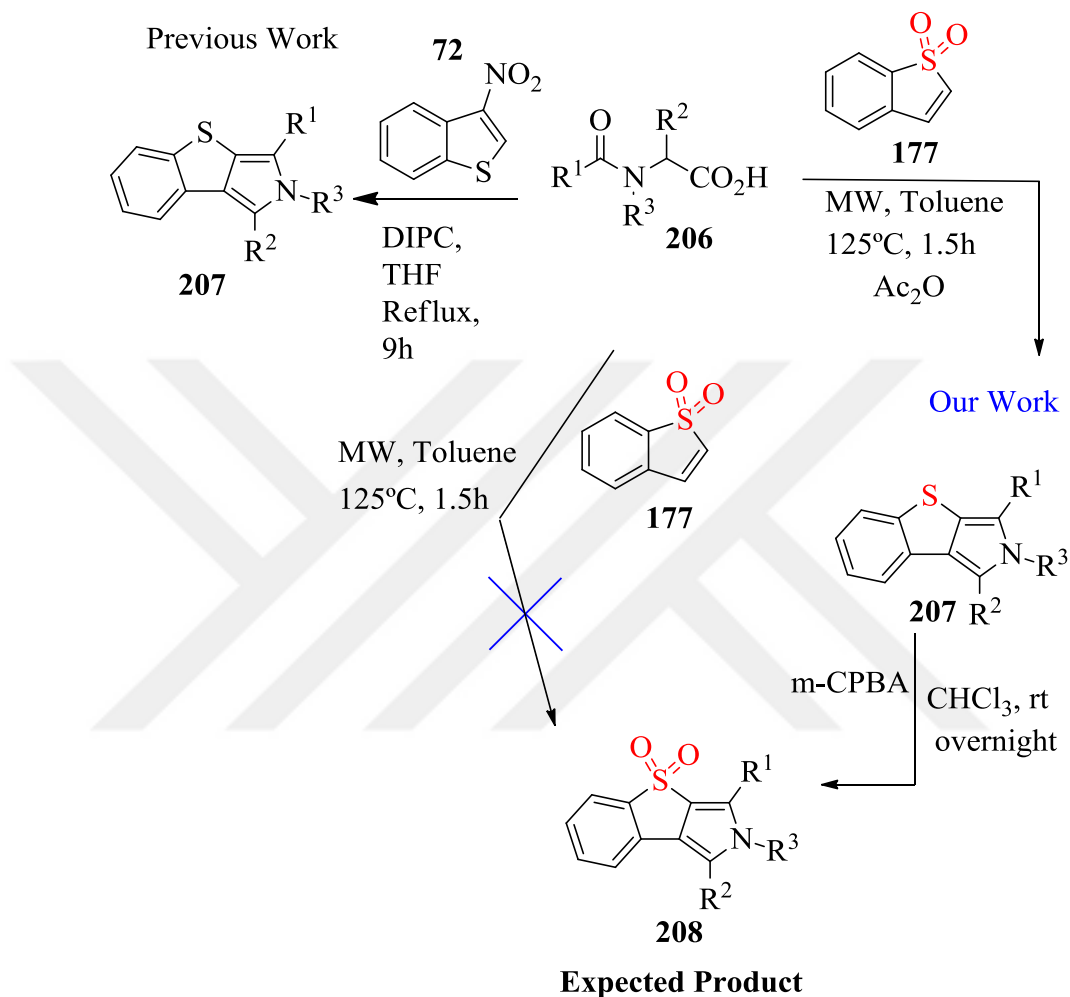
In addition, münchnone precursor **206** and benzo[*b*]thiophene **220** reactions tried in different conditions but all these experiments were unsuccessful and no fused pyrrole derivatives could be obtained.



Scheme 4.5 Münchnone **206** and benzo[*b*]thiophene **220** did not undergo reaction under the different conditions

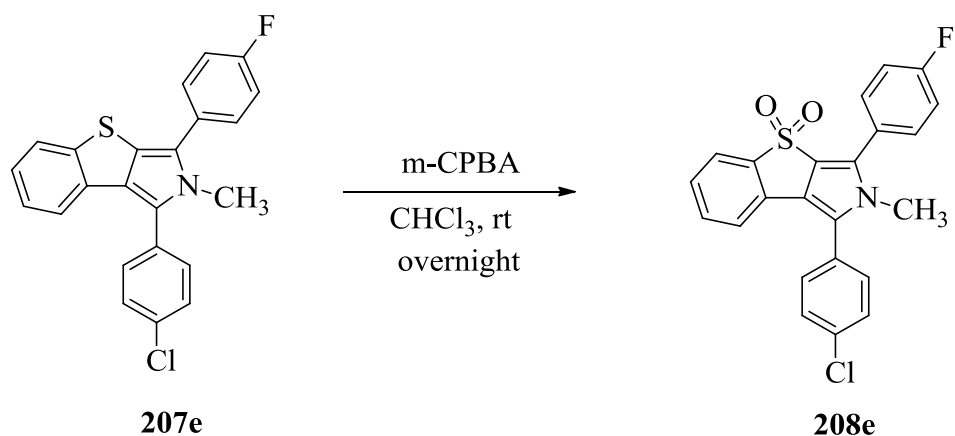
Gribble et al. (1998) synthesized benzo[4,5]thieno pyrrole derivatives **207** by reaction of münchnones generated *in situ* from cyclodehydration of the *N*-acyl amino acid **206** with *N,N'*-diisopropylcarbodiimide and nitrobenzo[*b*]thiophene **72**. In our work, cycloaddition reaction of münchnones which are generated *in situ* by

cyclodehydration of the *N*-(acyl)-*N*-methylglycine derivatives **206a-k** and *N*-acetyl-*N*-benzylalanine **206l** with acetic anhydride and benzo[*b*]thiophene 1,1-dioxide **177** accompanying deoxygenation of sulfone moiety gave rise to benzo[4,5]thienopyrrole derivatives **207**.



Scheme 4.6 Different strategies for the synthesis of fused pyrrole derivatives

In order to rationalize the work, the oxidation of sulfide **207e** into sulfone **208e** which was the anticipated product was performed with *m*-chloroperbenzoic (*m*-CPBA).



Scheme 4.7 *m*-CPBA oxidation of cycloadduct **207e**

The structure elucidation of the new sulfone **208e**, was performed by means of spectroscopic methods, especially by ^1H NMR, ^{13}C NMR, MS and X-Ray diffraction. The new product showed the symmetric and asymmetric stretching vibrations of SO_2 moiety at around 1150 and 1300 cm^{-1} , respectively in the IR spectra. The other proof of the generation of sulfone cycloadduct is the change of position of *N*- CH_3 protons in the ^1H NMR spectra. The methylic protons of sulfide cycloadduct **207e** have chemical shifts around the 3.67 ppm, however, the methylic protons of sulfone cycloadduct **208e** have chemical shifts around the 3.46 ppm.

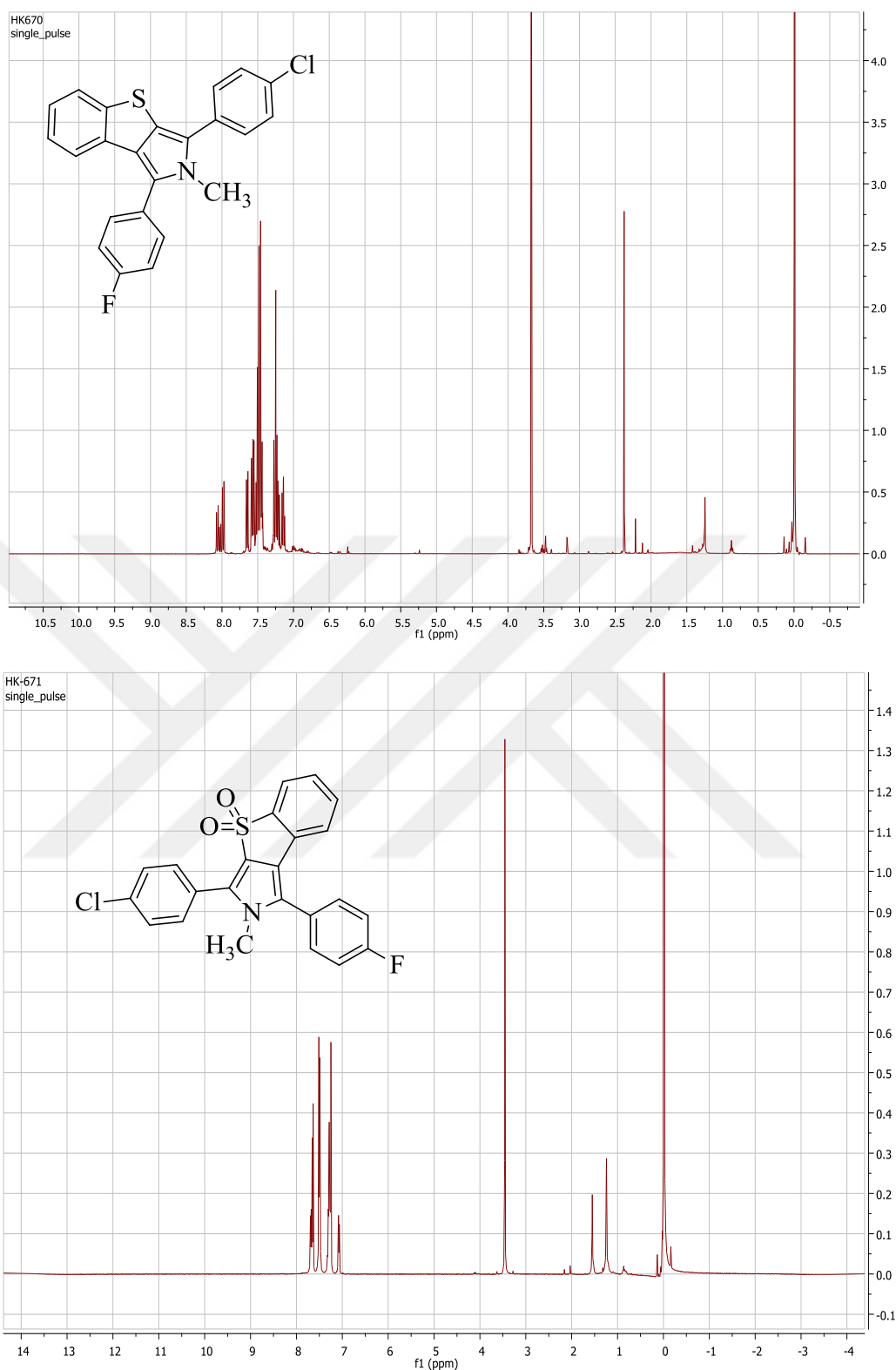
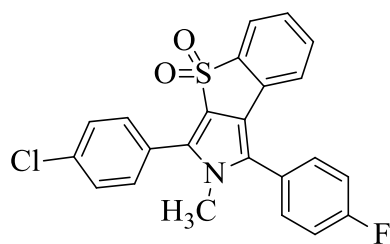
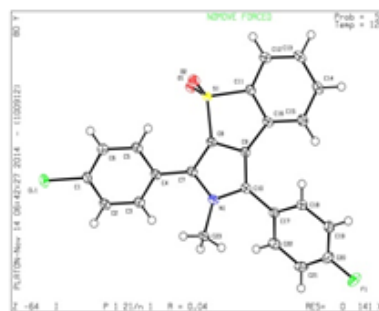


Figure 4.2 Comparing ¹H NMR of sulfide and sulfone cycloadduct 207e and 208e

Recrystallization of compound **208e** from a suitable solvent gave fine crystals and absolute stereochemistry of the compound **208e** was determined by X-Ray diffraction.



208e

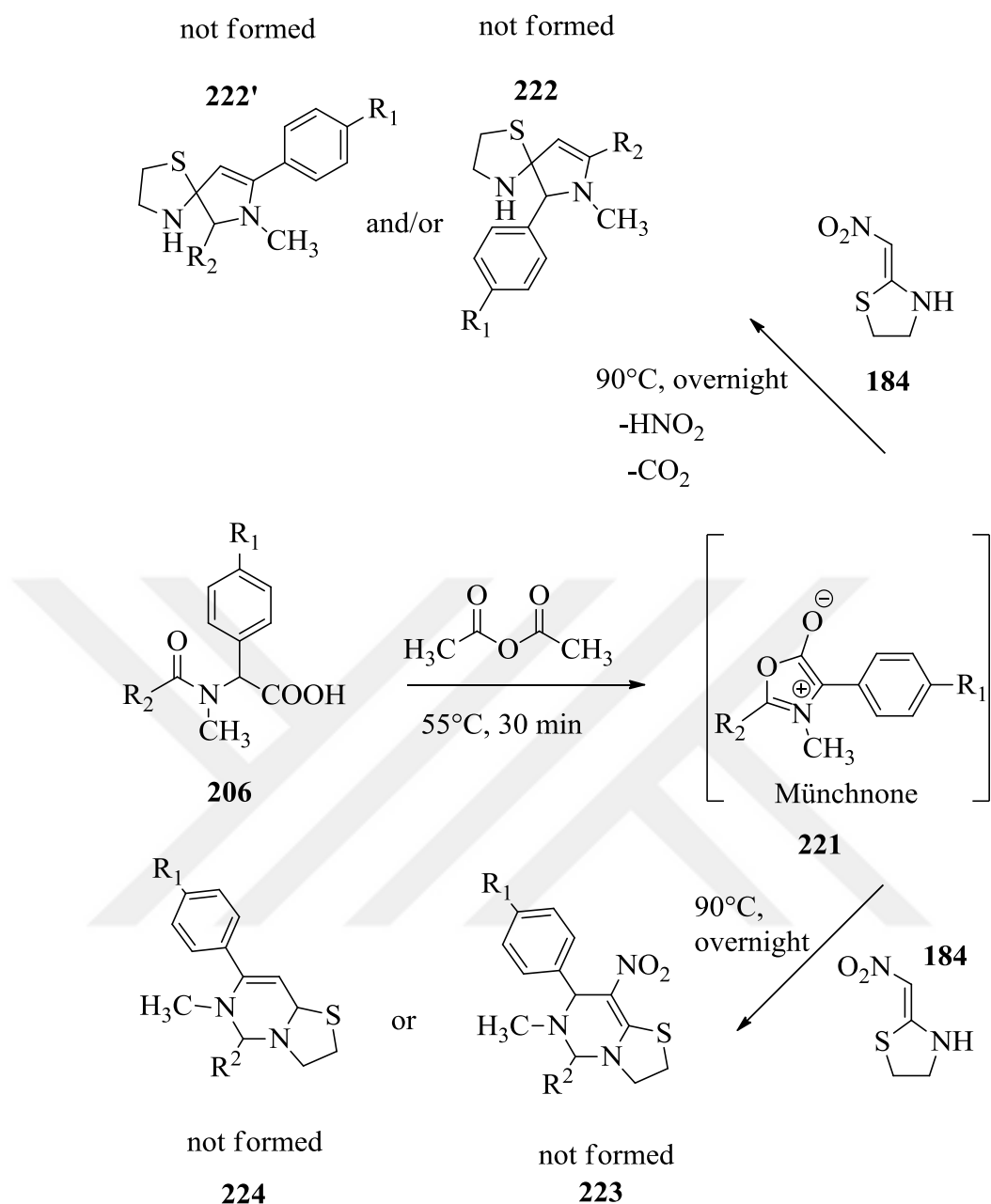


208e

Figure 4.3 X-Ray diffraction for compound **208e**

Part 2: Synthesis of (E)-1-(N,4-dimethylbenzamido)-1-(4-fluorophenyl)prop-1-en-2-yl acetate 209, 4-substitutedphenyl-N-methyl-N-(4-substitutedbenzoyl)benzamides 210 and p-substituted benzoic acids 211

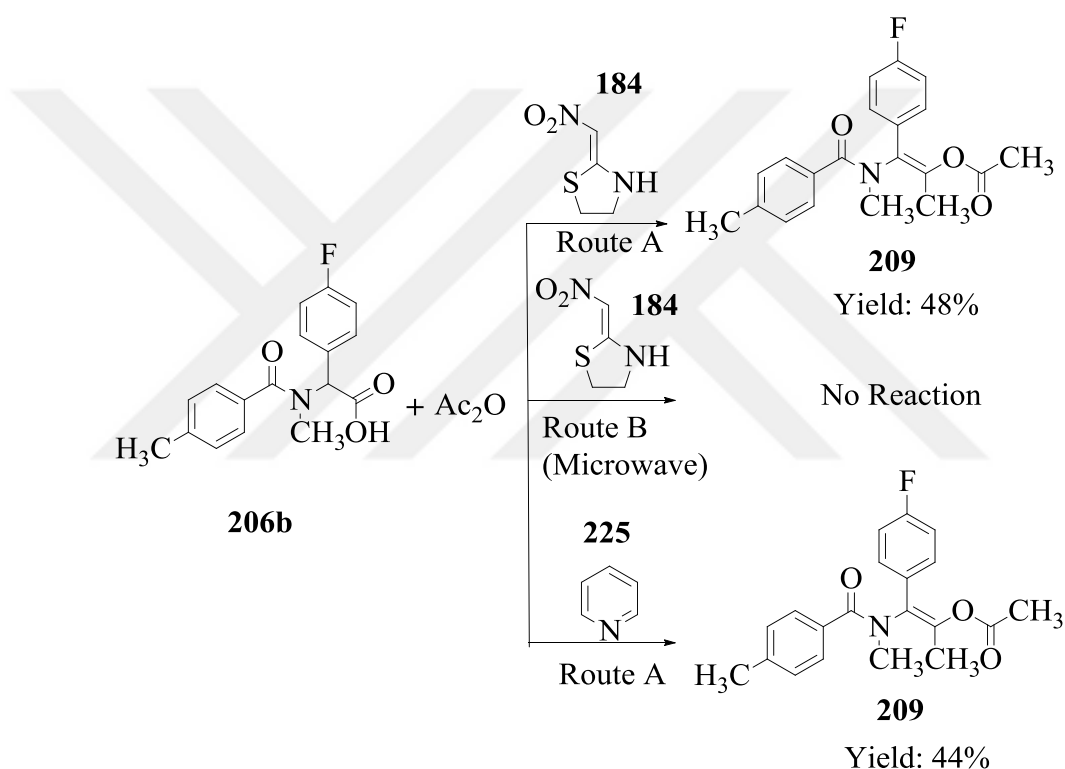
Several heterocyclic systems have been synthesized by the cycloaddition of münchnones, generated *in situ* from the corresponding N-acylamino acids with carbon-carbon double bonds of a suitable dipolarophiles. In this perspective, the cycloaddition reactions of münchnones **221** (1,3-dipoles) with 2-nitromethylene thiazolidine **184** (as an electron deficient dipolarophile) have been tried to furnish spiro structures through HNO₂ and CO₂ eliminations or fused heterocycles.



Scheme 4.8 Possible products of münchnone **221**-2-nitromethylenethiazolidine **184** 1,3-dipolar cycloaddition leading to spiro or fused heterocycles.

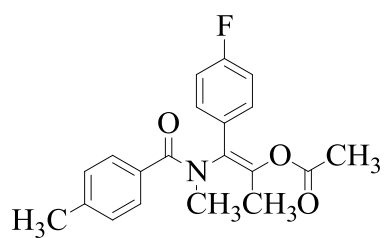
Upon initial examination of NMR, IR and HRMS data of the reaction products, we noticed that no expected spiro structures or fused heterocycles were formed. In this regard, ¹H NMR spectra did not give relevant methylene protons of 2-nitromethylenethiazolidine **184** and mass spectra did not exhibit any molecular ions peaks of anticipated cycloadducts **222-224**, as well.

Although 2-nitromethylene thiazolidine **184** seem to show dipolarophile character at double bond, it might have behaved like a base through its imine tautomeric form. Instead of spiro or fused compounds, the reaction between 2-(*N*,4-dimethylbenzamido)-2-(4-fluorophenyl)acetic acid **206b** which was used without further purification and 2-nitromethylene thiazolidine **184** in the acetic acid at 90°C results an enol ester compound **209** but no reaction occurred under microwave heating. The same reaction has been tried with pyridine **225** instead of 2-nitromethylene thiazolidine **184** under same reaction conditions and gave same enol ester form **209** in moderate yields.

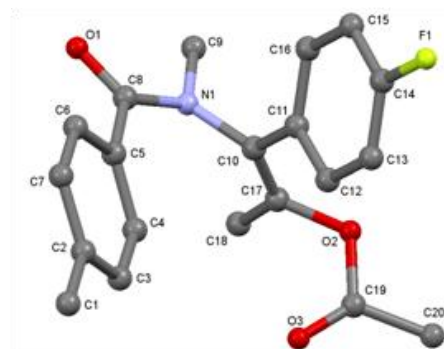


Scheme 4.9 Reactions between **206b** and acetic anhydride in the presence of 2-nitromethylenethiazolidine **184** and pyridine to afford enol ester **209**

In the IR spectra of **209**, two carbonyl ($\text{C}=\text{O}$) absorptions appeared at around 1745 and 1647 cm^{-1} and proton NMR gave four singlet peaks between 3.31-1.98 ppm, one of them is of *p*-tolyl methyl protons and spectral data were not enough for the characterization of this compound. After recrystallization of compound **209** from suitable solvent gave fine crystals and we were able to get full characterization of the structure by means of X-ray single crystal data.



209

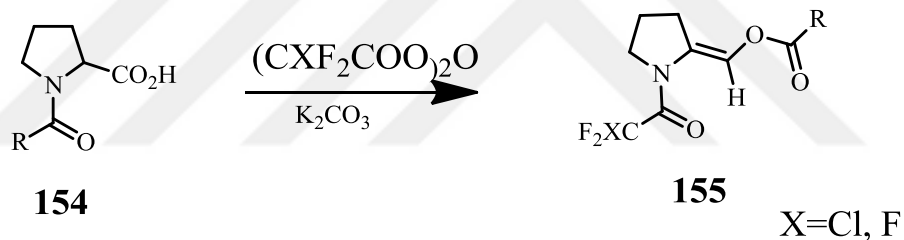


209

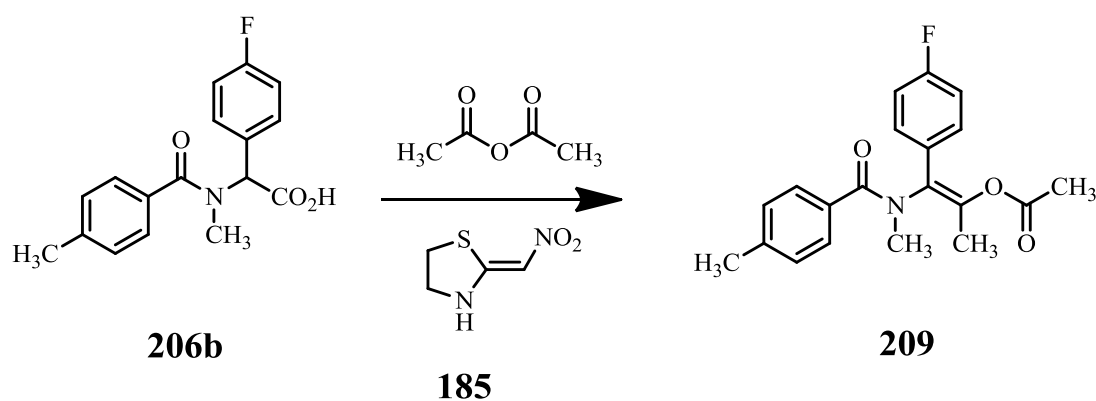
Figure 4.4 X-Ray ORTEP view of enol ester **209**

A similar product obtained through a rearrangement process with *N*-acyl prolines in the presence of inorganic bases such as K_2CO_3 , Na_2CO_3 was reported by Saeki (2009) group.

Previous work



Present work

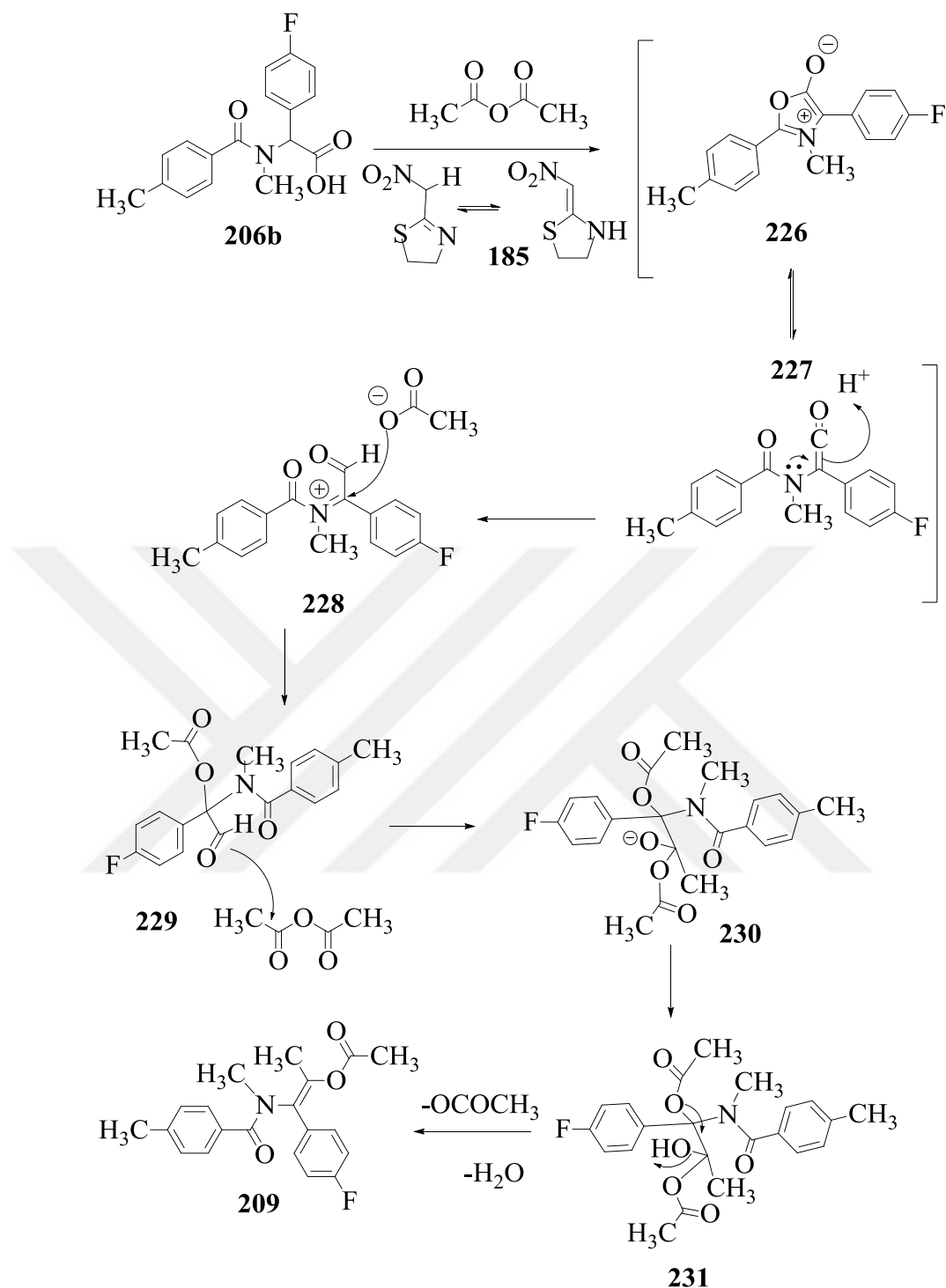


Scheme 4.10 Formation of enol ester with using different strategies

Therefore, this enol ester possibly through a Dakin-West type reaction pathway depicted below at which tautomeric form of 2-nitromethylenethiazolidine **184**

behaves as a base and we anticipated Dakin-West type reaction mechanism for this enol ester product. Initially, 2-(*N*,4-Dimethylbenzamido)-2-(4-fluorophenyl)acetic acid **206b** reacted with acetic anhydride which was used a cyclodehydration agent and solvent to give a mesoionic 1,3-oxazolium-5-olate form **226**. Intermediate **226** was in the equilibrium in ketene whose formation could be facilitated by the elevated temperature of heating acetic anhydride. The ketene **227** form isomerize to the aldehyde **228**, then converted to the intermediate forms. After oxygenating this intermediate forms afforded to enol ester form **209**.





Scheme 4.11 Plausible mechanism for the synthesis enol ester **209**

We have utilized different reaction conditions for other amino acids to obtain a variety of enol ester **209**, but all the attempts failed, that is, no ester products could form. But, however, when we used **206d**, **206f**, **206h**, **206i** and **206j** as starting aminoacids, we obtained some new benzoyl, methyl substituted benzamides **210d**,

210f, 210h, 210i, 210j as the only products. IR spectra showed again two carbonyl absorption between 1701 and 1651 cm^{-1} . But, ^1H NMR spectra did not give four singlet peaks. One singlet peak appeared at approximately 3.50 ppm (*N*-CH₃).

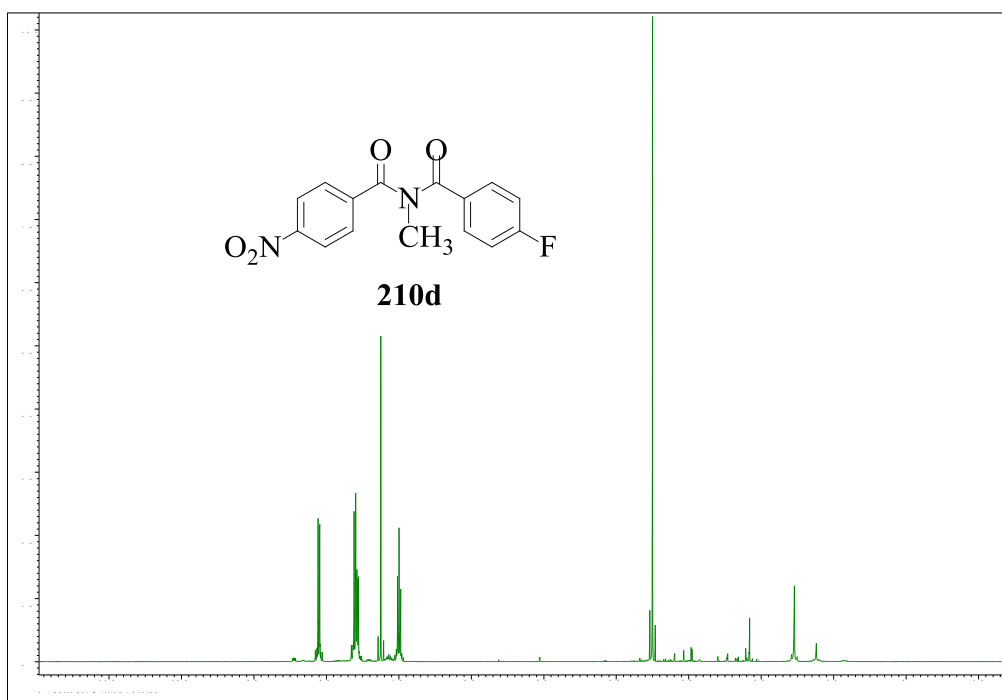
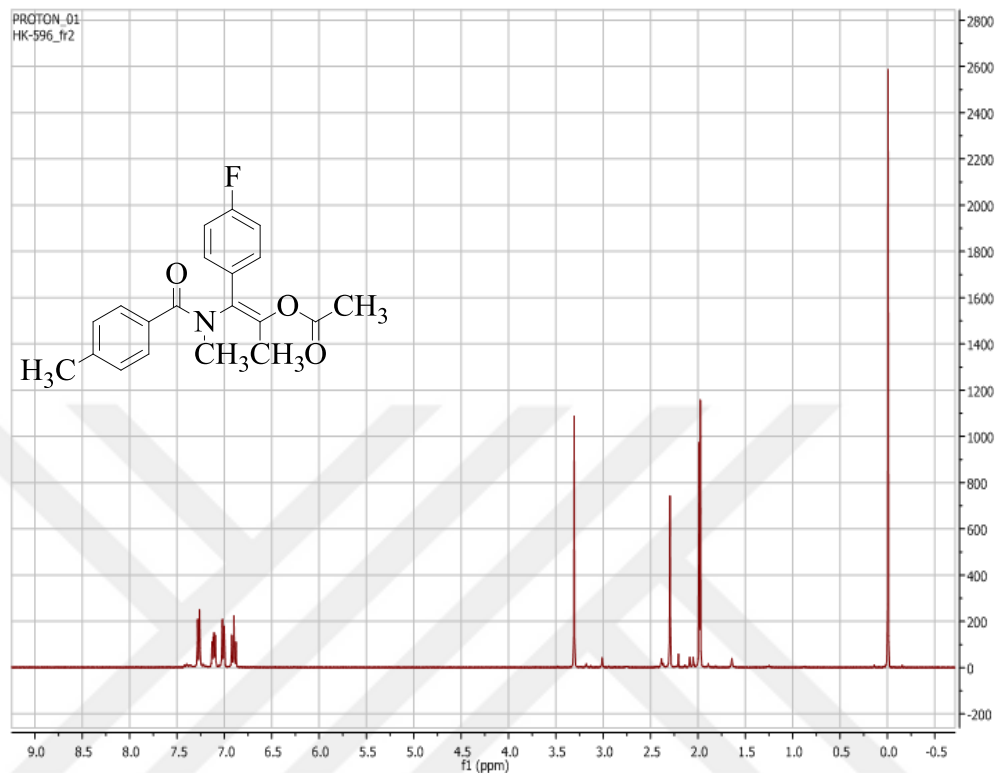
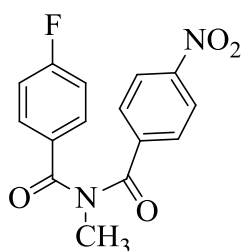
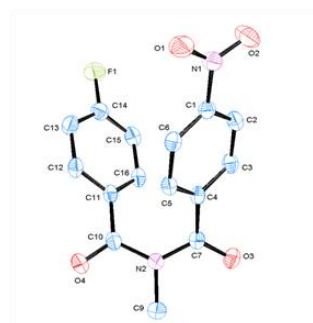


Figure 4.5 ^1H NMR Spectrum of compounds **209** and **210d**

Other amino acids (**206f**, **206h**, **206i**, **206j**) gave the similar products and similar ^1H NMR and ^{13}C NMR resonances in their spectra. This much spectral data were enough for explaining of the structures of the products. After obtaining fine crystals, we were able to establish exact structure of **210d** by X-ray diffraction data.



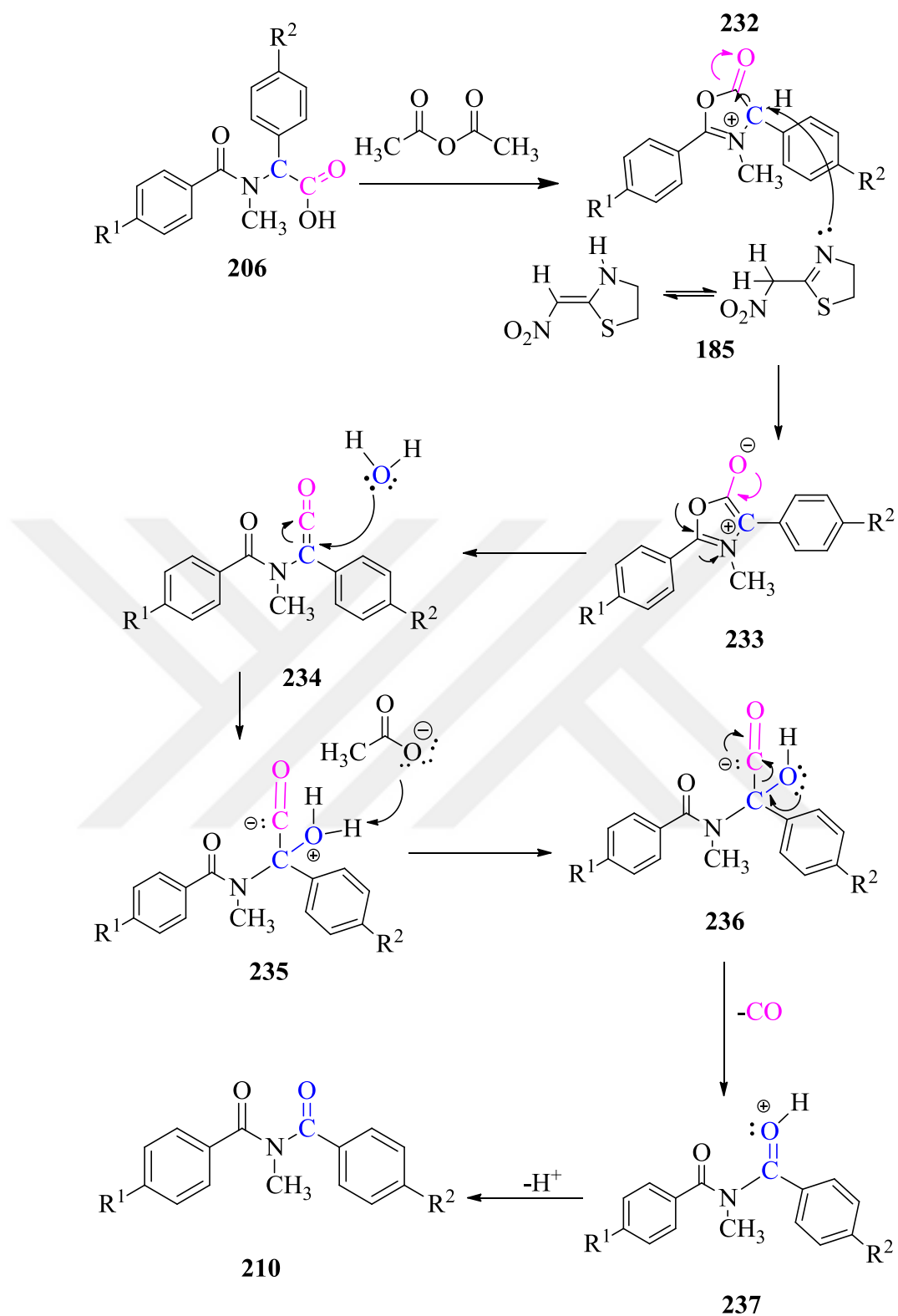
210d



210d

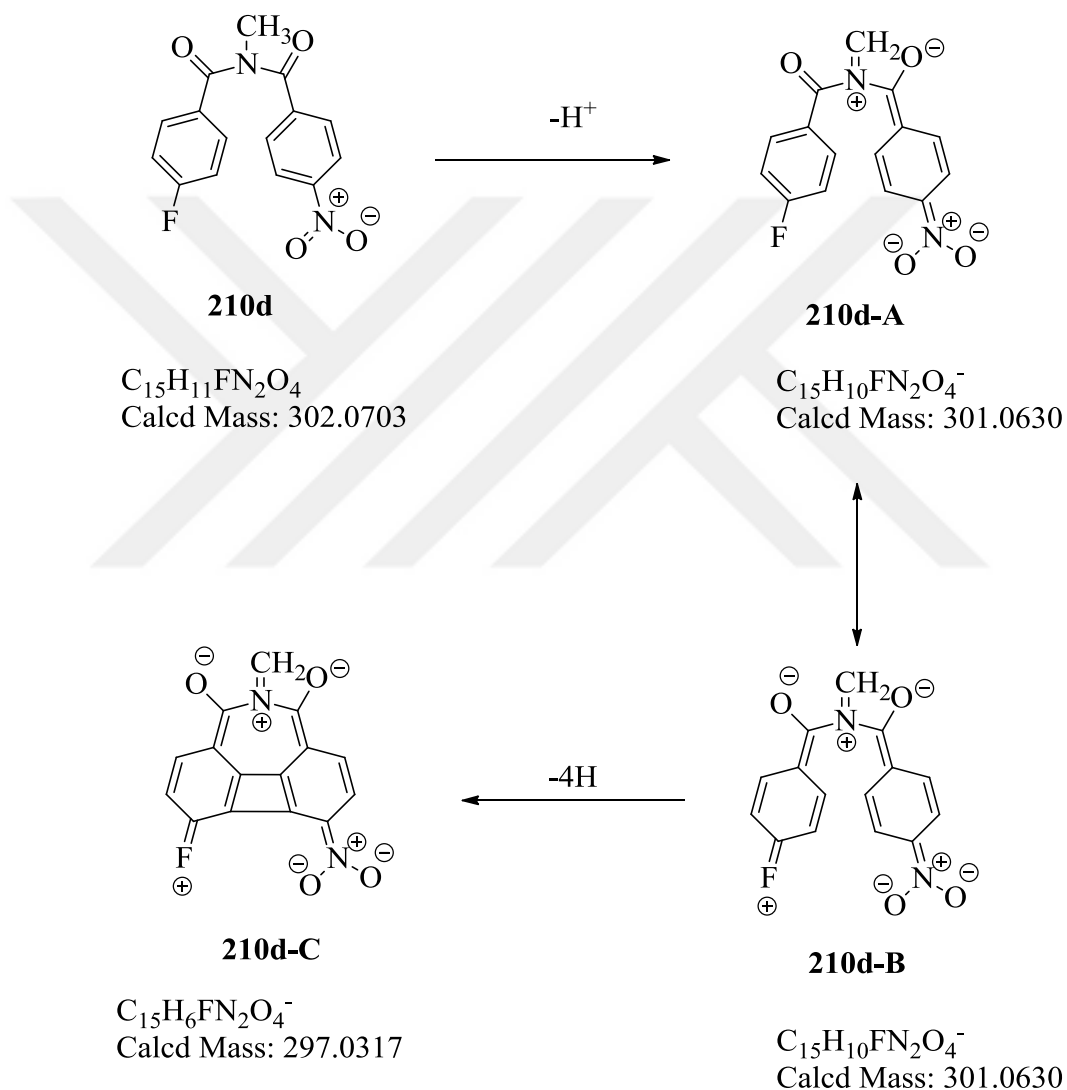
Figure 4.6 X-Ray ORTEP view of **210d**

A possible reaction mechanism at which, after münchnone formation, the ketene form **234** was likely attacked by a water molecule and a subsequent carbon monoxide release may be considered.



Scheme 4.12 Possible reaction mechanism involving carbon monoxide release leading to substituted benzamides **210**

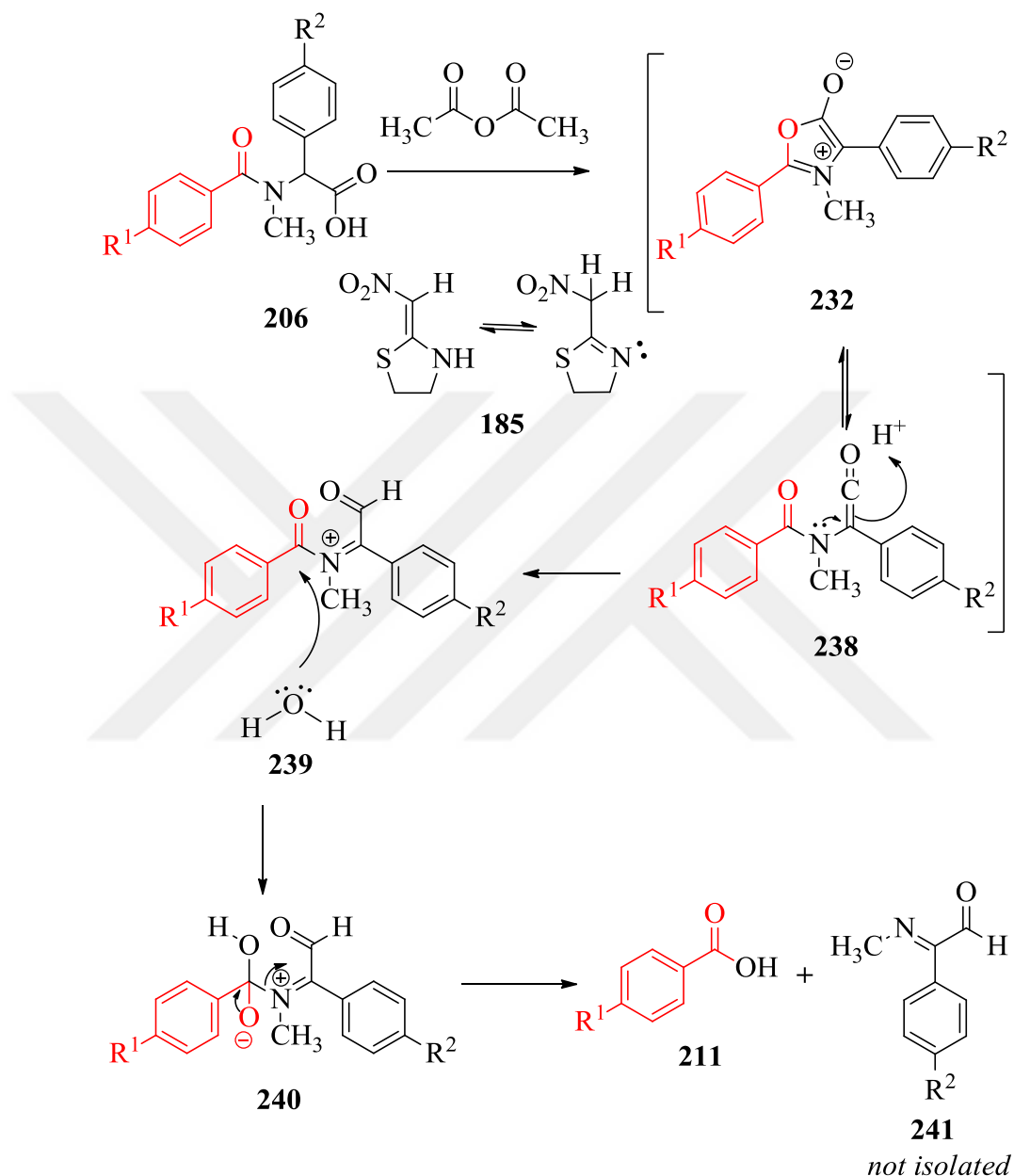
Upon examination of the LC-MS spectrum of amide **210d**, we observed a peak related to $[M-4H]$ under the ES^- mode (whilst compound can not be ionized under ES^+ condition) which might be attributed to **210d-C** having full delocalization through the entire molecule caused by a π - π stacking (even though fluorine has plus charge on it which is not a desirable resonance structure) shown below (Scheme 4.13). Polar- π interactions between stacked aryl groups were reported (Hunter, 1990; Cozzi, 1992, 1993, 2008).



Scheme 4.13 Structure of ionic fragment at m/z 297 of **210d**

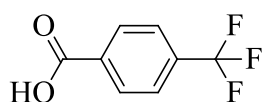
In addition, *N*-acylamino acids **206** and 2-nitromethylene thiazolidine **184** in acetic anhydride were irradiated at 0-150 W for 45 min in closed glass vial in a CEM microwave synthesiser at 80 °C to obtain a variety of enol ester **209**, but we obtained

benzoyl, methyl substituted benzamides **210** and carboxylic acid derivatives **211**. This acid derivatives **211** also obtained through a possible Dakin-West reaction pathway shown below (Scheme 4. 14).

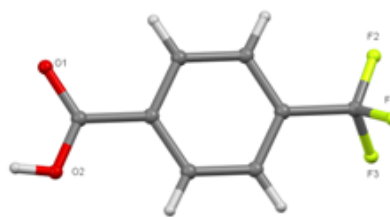


Scheme 4.14 Possible reaction mechanism leading to 4-substituted benzoic acids **211**

IR spectra showed one carbonyl absorption at around 1685 cm^{-1} . But, ^1H NMR spectra did not give any singlet peak or peaks. In order to identify the carboxylic acid formed above exactly, X-ray diffraction data was obtained using a fine crystal.



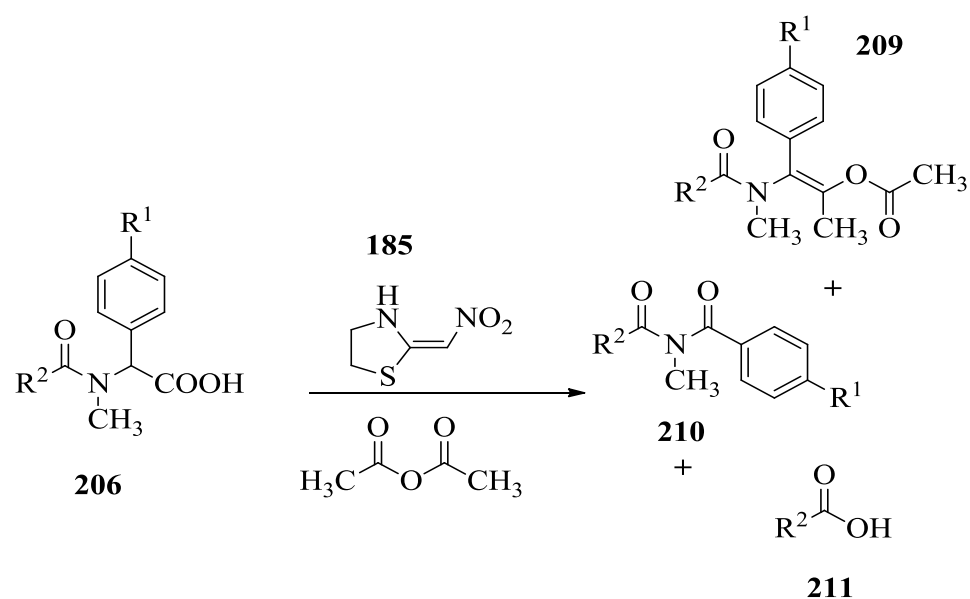
211f



211f

Figure 4.7 An ORTEP projection of compound **211f**

Eleven amino acids (**206a-k**) has been used to prepare the münchnone precursors which were subsequently reacted with 2-nitromethylene thiazolidine **184** in acetic anhydride under conventional and microwave heating methods. Only conventional heating method gave enol ester form **209**. Only conventional heating applied to 2-(4-fluorophenyl)-2-(*N*-methylbenzamido)acetic acid **206a** and 2-(4-fluorophenyl)-2-(*N*-methyl-3-phenylpropanamido)acetic acid **206g** gave the benzoic acid **211a** and 3-phenylpropanoic acid **211g**. 2-(4-methoxyphenyl)-2-(*N*-methyl-4-nitrobenzamido)acetic acid **206i** and 2-(4-methoxyphenyl)-2-(*N*-methyl-4-(trifluoromethyl)benzamido)acetic acid **206j** were utilized under microwave heating method and observed only substituted benzamides. For **206c**, **206d**, **206e**, **206f** and **206h** as starting amino acids and applied both conventional heating and microwave heating methods.



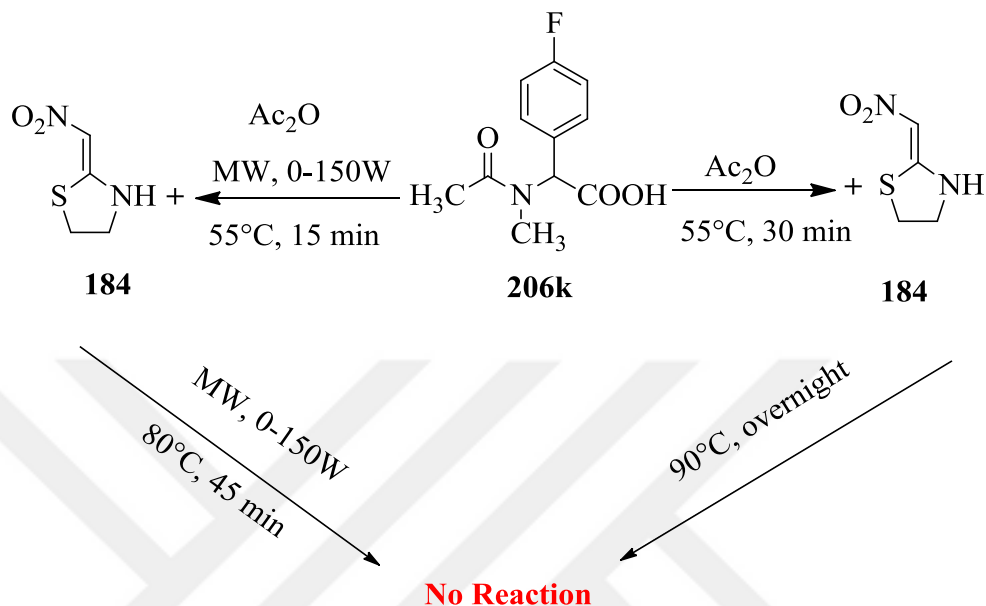
Entry	Substrate	R ¹	R ²	Product	Route A Yield %	Route B Yield %
1	206a	F	C ₆ H ₅	211a	39	—
2	206b	F	p-CH ₃ -C ₆ H ₄	209	48	No Reaction
3	206c	F	p-CH ₃ O-C ₆ H ₄	211c	83	54
4	206d	F	p-NO ₂ -C ₆ H ₄	210d, 211d	(210d) 34	(211d) 66
5	206e	F	p-Cl-C ₆ H ₄	211e	83	36
6	206f	F	p-CF ₃ -C ₆ H ₄	210f, 211f	(211f) 70 (210f) 16	(211f) 19
7	206g	F	C ₆ H ₅ -CH ₂ CH ₂	211g	75	—
8	206h	CH ₃ O	p-CH ₃ -C ₆ H ₄	210h, 211b	(211b) 66	(211b) 52 (210h) 19
9	206i	CH ₃ O	p-NO ₂ -C ₆ H ₄	210i	—	21
10	206j	CH ₃ O	p-CF ₃ -C ₆ H ₄	210j	—	20
11	206k	F	CH ₃	210k	No Reaction	No Reaction

Only Route A was applied in entry 1 and 7

Only Route B was applied in entry 9 and 10

Table 4.2 Products obtained from the reaction between Münchnone precursors **206** and acetic anhydride in the presence of 2-nitromethylenethiazolidine **184** with yields

In order to rationalize whether aromatic substituent on nitrogen effects the product formation, we used *N*-acetyl substituted amino acid **206k** both under classical and microwave heating and observed no reaction at all, confirming that aromatic group has the major impact on this reaction.



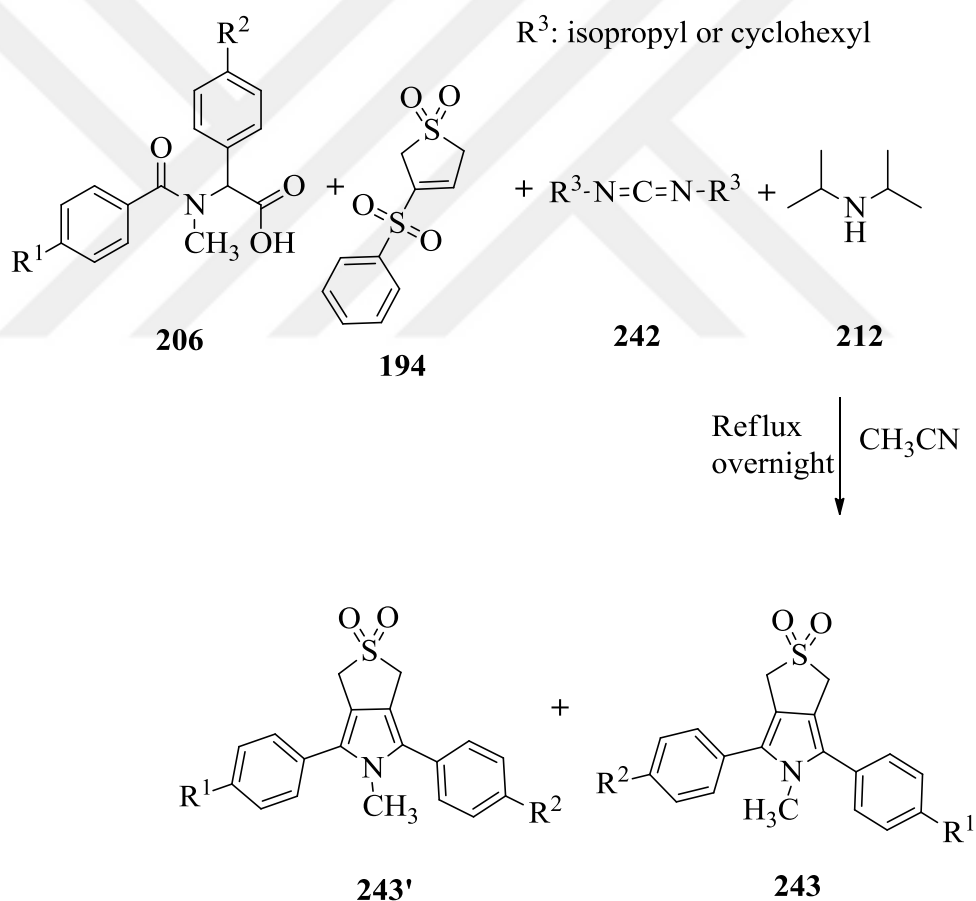
Scheme 4.15 *N*-Acetyl-*N*-methyl substituted amino acid **206k** did not undergo reaction under the specified conditions

Part 3: Synthesis of *N*-acylureas

Münchnones, so called, 1,3-oxazolium-5-olates, are among the five-membered mesoionic compounds which can be easily prepared by cyclodehydration of *N*-substituted-*N*-acyl- α -amino acids with *N,N'*-diisopropylcarbodiimide **163** or *N,N'*-dicyclohexylcarbodiimide **160**. They are utilized in the synthesis of many valuable heterocycles such as substituted pyrroles through 1,3-dipolar cycloaddition with a wide range of double or triple bonded electron-deficient dipolarophilic reagents. Also, sulfolene derivatives are useful dipolarophiles and precursors to 1,3-dienes with predictable double bond geometry.

For this reason, we have been focused on the cycloaddition reactions of münchnones, generated *in situ* from the corresponding *N*-acylamino acids **206** using *N,N'*-diisopropylcarbodiimide **163** or *N,N'*-dicyclohexylcarbodiimide **160** as the dehydrating agent with 3-(phenylsulfonyl)-2,5-dihydrothiophene 1,1-dioxide **194** in

the presence of a base, diispropyl amine **212**, in acetonitrile at reflux temperature to furnish new pyrrole derivatives. Upon initial examination of the NMR, IR and HRMS data of the products, we understood that the expected fused structures through PhSO₂ and CO₂ release, Matsukubo (1975), and Fisk (2007), (Scheme 4.16), did not formed. In this regard, the symmetric and asymmetric stretching vibrations of SO₂ moiety were not observed at around 1150 and 1300 cm⁻¹, respectively in the IR spectra. Also, ¹H NMR spectra did not give relevant methylene protons of sulfolene and mass spectra did not exhibit any molecular ions peaks of anticipated cycloadducts, as well. The attempted cycloaddition reactions of münchnones with this dipolarophile failed to obtain expected cycloadduct. But, unfortunately, the change of reaction conditions did not give adequate results.



Scheme 4.16 Possible products of Münchnone-3-(phenylsulfonyl)-2,5-dihydrothiophene 1,1-dioxide **194** 1,3-dipolar cycloaddition leading to fused heterocycles.

Instead of symmetric and asymmetric stretching vibrations of SO₂ moiety, IR spectra showed one carbonyl absorption between 1720 and 1690 cm⁻¹. Also, ¹H NMR spectra showed one singlet peak between 6.70 and 6.00 ppm, two multiplet peaks between 4.50 and 3.75 ppm (Scheme 4. 8). These spectral data were not enough for full structural characterization of these compounds. But, however, we were able to obtain a fine crystals of compounds **214e** from suitable solvents, X-ray diffraction ORTEP view revealed the structures assigned as depicted in Scheme 4. 9.

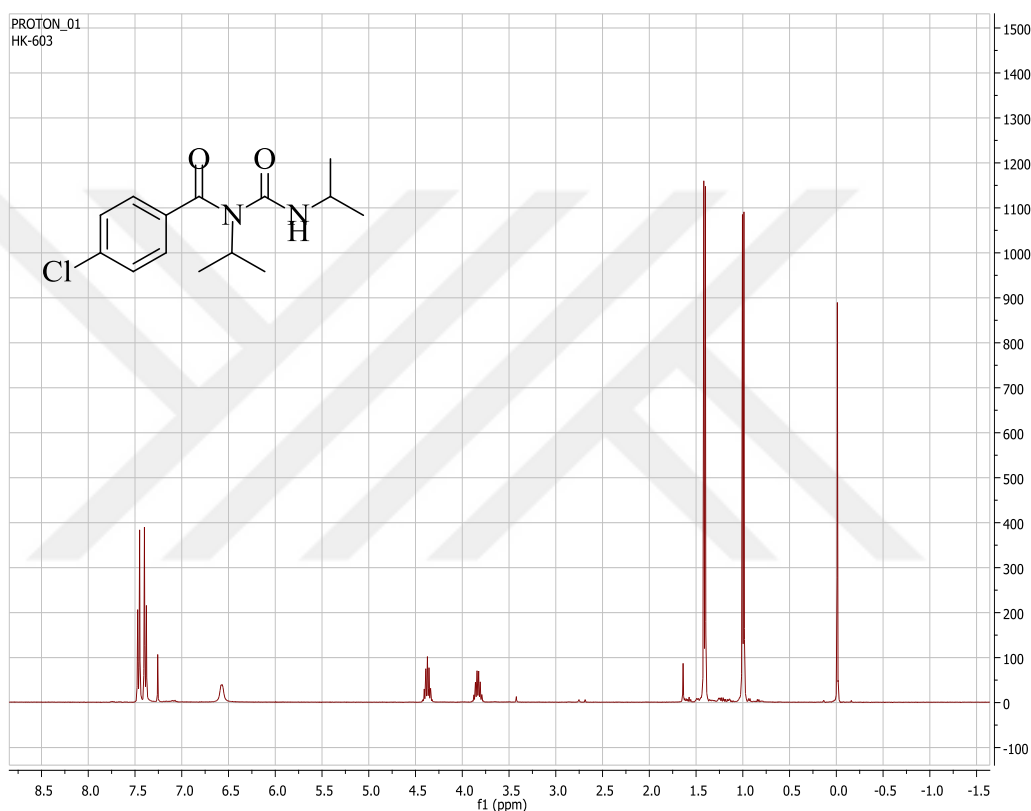


Figure 4.8 ¹H NMR spectrum of compounds **213d** and **214d**

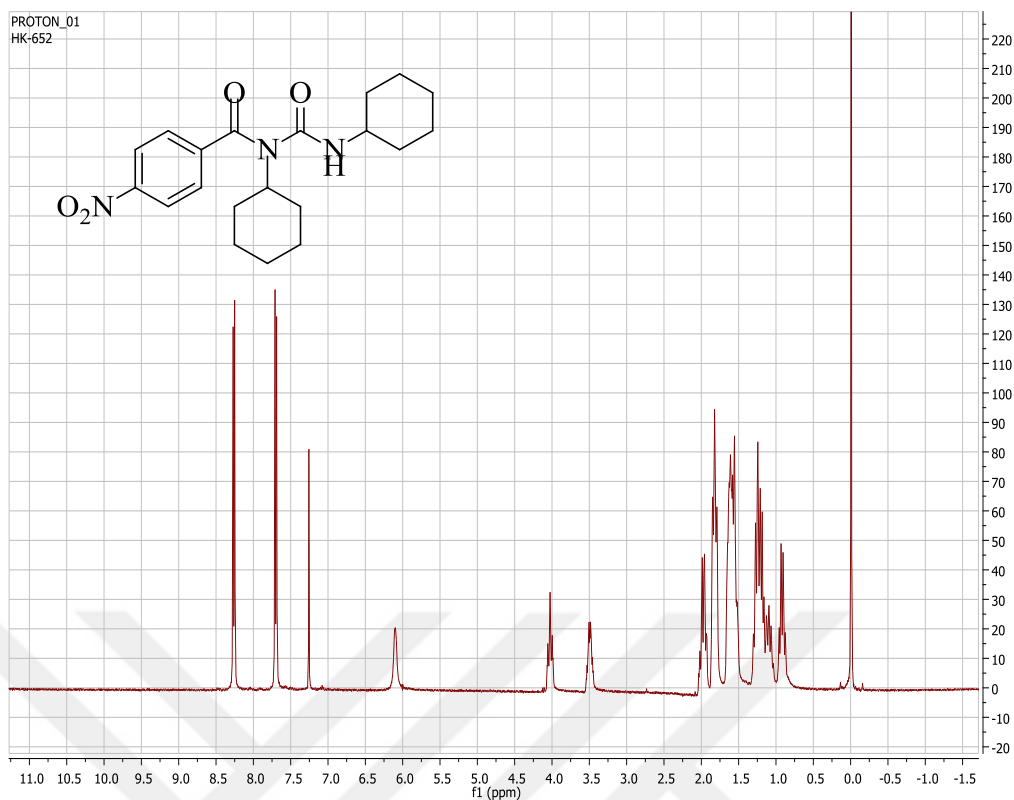
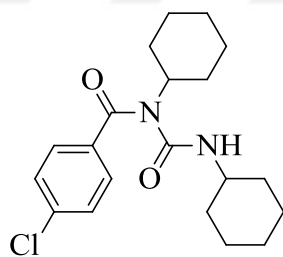
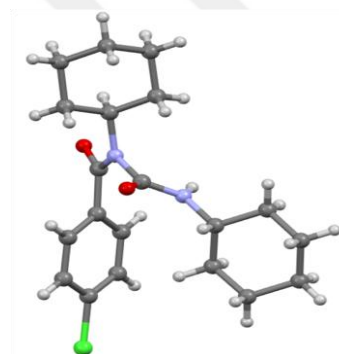


Figure 4.9 Cont'd.



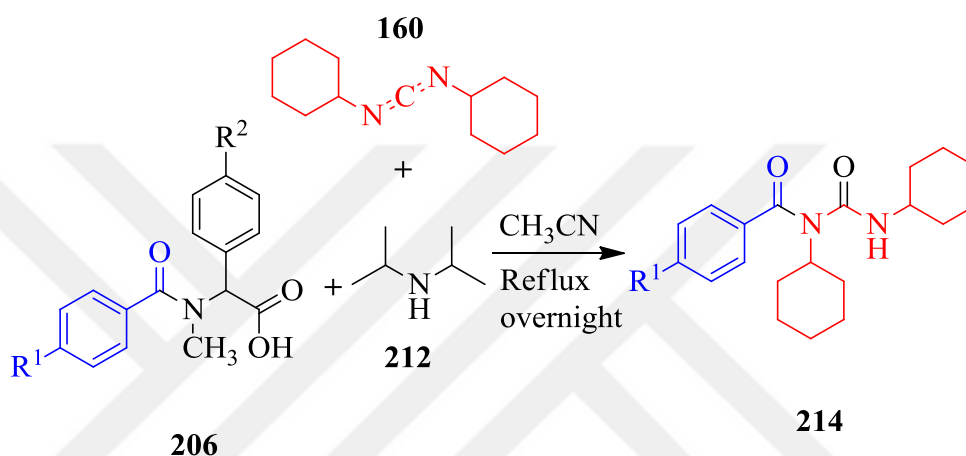
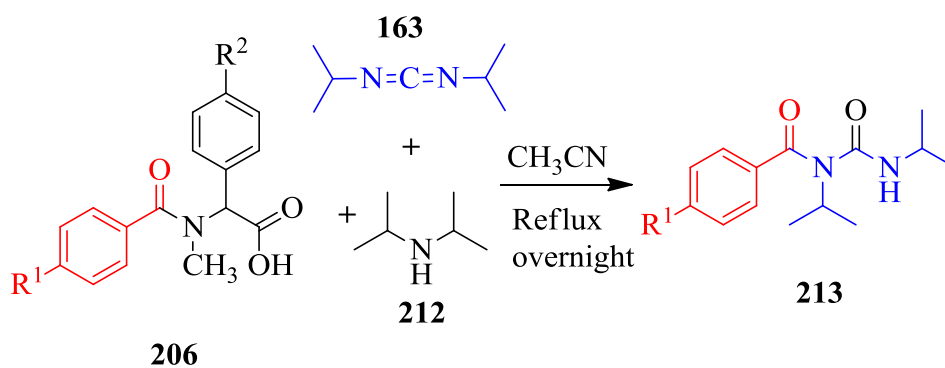
214e



214e

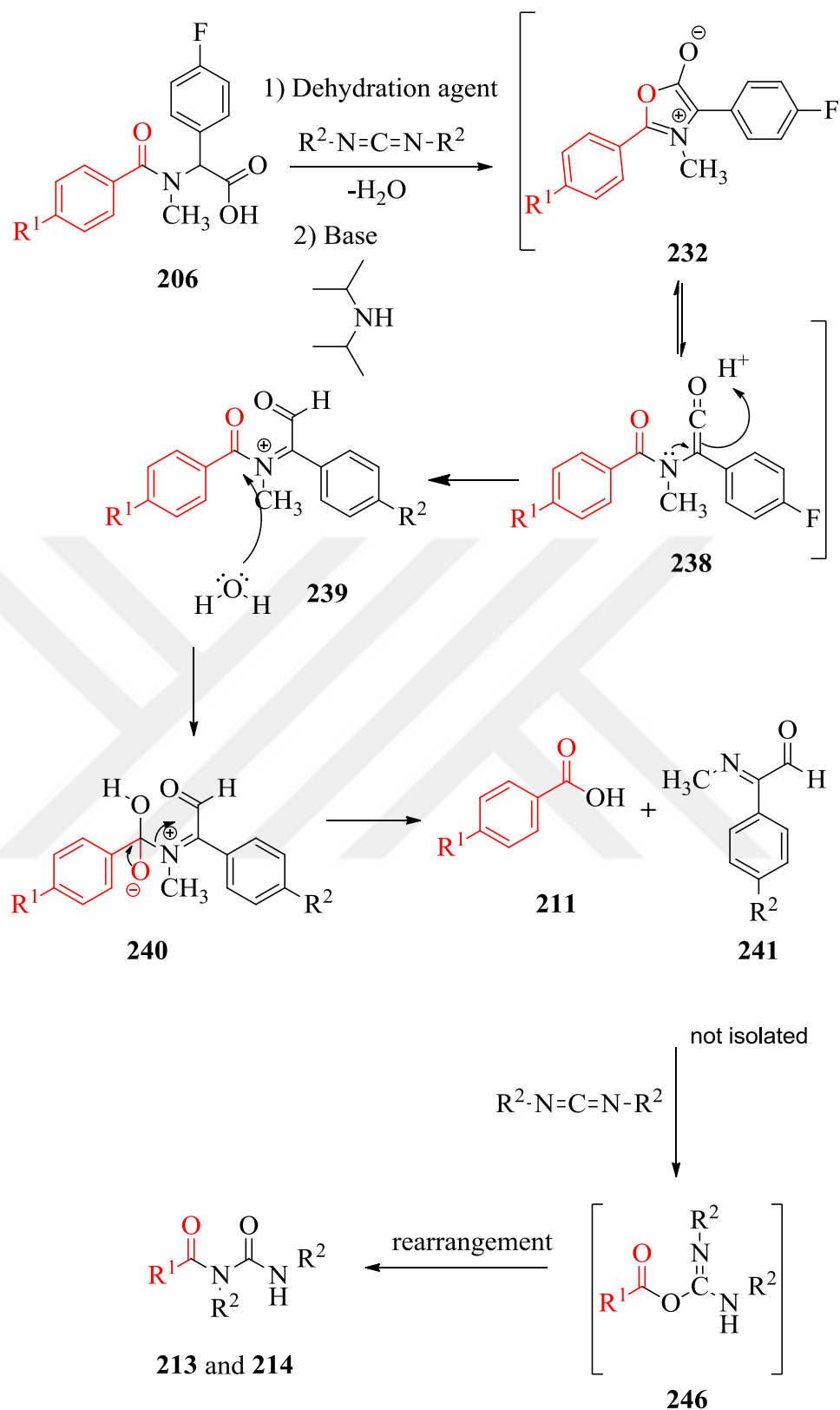
Figure 4.10 An ORTEP projection of compound **214e**

Due to this spectral evidences, we have been directed into reactions of münchnone precursors with *N,N'*-diisopropylcarbodiimide **163** and *N,N'*-dicyclohexylcarbodiimide **160** in the presence of diisopropyl amine to give *N*-acylurea derivatives without using any sulfolene **194**. On the other hand, carbodiimide derivatives which are effective reagents in the cyclodehydration for the formation of münchnones, are used preparation *N*-acylurea derivatives.



Scheme 4.17 Synthesis of *N*-acylurea derivatives **213** and **214**

On the basis of these results, we anticipated Dakin-West type reaction mechanism for this *N*-acylurea products. Initially, *N*-acylamino acids **206** reacted with carbodiimides to give a mesoionic 1,3-oxazolium-5-olate form **232**. Intermediate **232** was in the equilibrium in ketene whose formation could be facilitated by the elevated temperature of heating acetonitrile. The ketene form **238** isomerize to the aldehyde **239**, then aldehyde **239** was attacked by a water molecule converted to the intermediate form **240**. After that, carboxylic acid **211** and imine form generated **241**. We did not isolated imine form **241**. Finally, excess carbodiimide gave reaction with carboxylic acid **211**, namely, acyl transfer leads to the corresponding *N*-acylureas **213** and **214**.



Scheme 4.118 Plausible reaction mechanism of *N*-acylurea derivatives **213** and **214**

5. CONCLUSION

In summary, the first part of the thesis, microwave assisted 1,3-dipolar cycloaddition reaction between münchnones which were synthesized according to literature and benzo[*b*]thiophene 1,1-dioxide was conducted and the deoxygenation of sulfone moiety was accompanied. Novel fused pyrrole derivatives were obtained. In order to rationalize the work, the oxidation of sulfide into sulfone, the anticipated product was obtained. The structure of fused benzo[4,5]thieno[2,3-*c*]pyrrole derivatives and fused benzo[4,5]thieno[2,3-*c*]pyrrole 4,4-dioxide were identified by the IR, ¹H, ¹³C NMR, MASS spectra and X-Ray diffraction.

In the second part, we have demonstrated that a Dakin-West type transformation occurred in the reaction between münchnone precursors (amino acids) and acetic anhydride in the presence of 2-nitromethylenethiazolidine which was likely acting as a base through its enamine tautomer to afford an enol ester. To our best knowledge (SciFinder Scholar, Web of Science), 2-nitromethylenethiazolidine has not been reported in the literature to employ in organic synthesis as a base. The structures of *E*-1-(*N*,4-dimethylbenzamido)-1-(4-fluorophenyl)prop-1-en-2-yl acetate **209**, 4-substituted-*N*-methyl-*N*-(4-substitutedbenzoyl)benzamides **210** and substituted benzoic acids **211**, were elucidated by the ¹H, ¹³C NMR, MASS spectra, X-Ray diffraction and IR spectra.

In the last part, a novel efficient route to give *N*-acylurea derivatives was described by the reaction between münchnone precursors with carbodiimides in the presence of a base. The structure of these *N*-acylureas were characterized by means of IR, ¹H and ¹³C NMR, X-ray diffraction data and physical characteristics.

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APPENDICES

7. APPENDICES

Appendix A

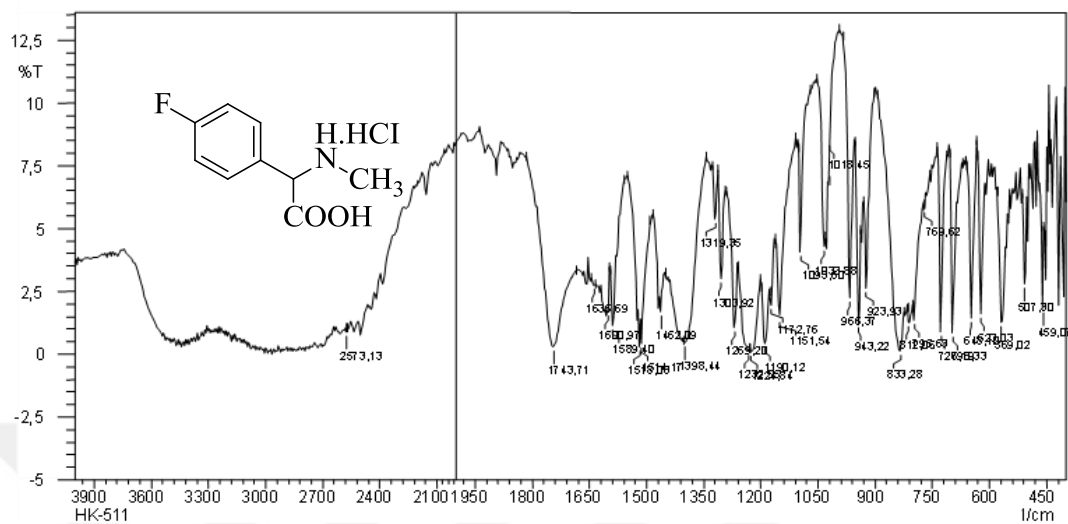


Figure A.1 IR Spectrum of compound 204a

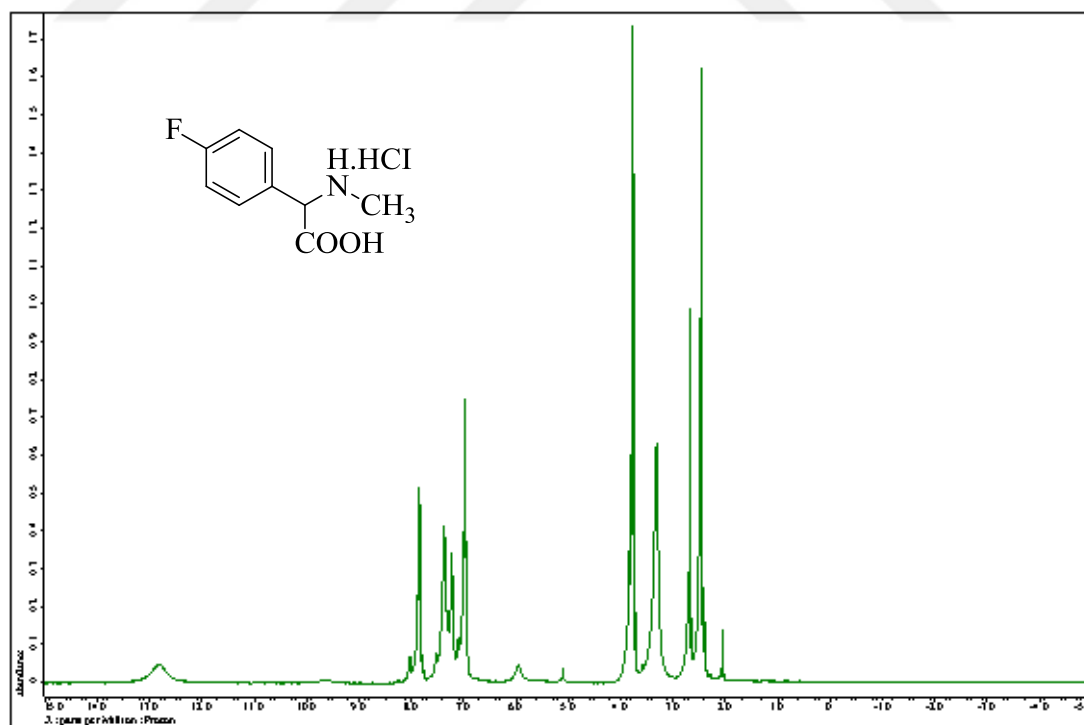


Figure A.2 ¹H NMR Spectrum of compound 204a

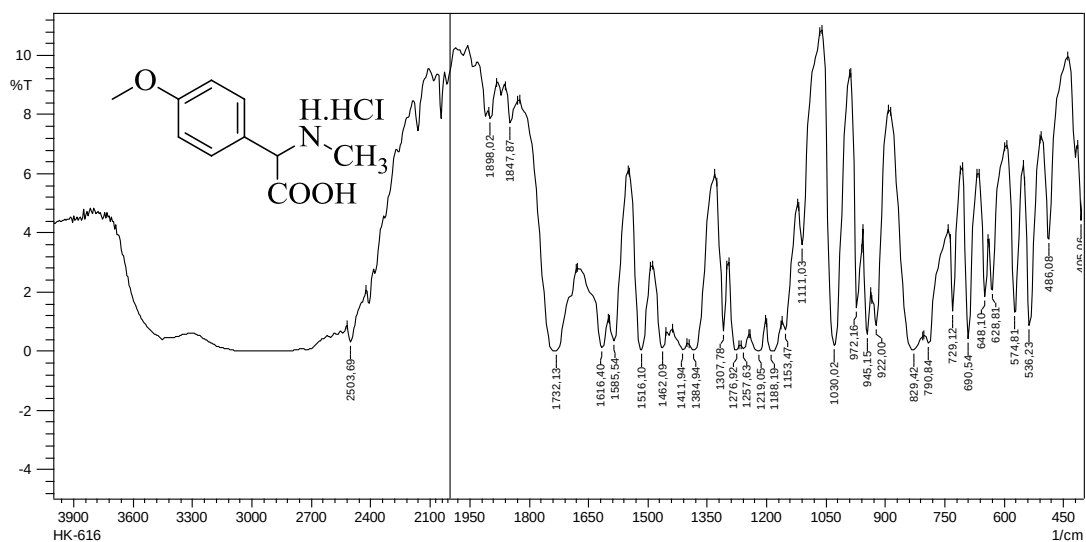


Figure A.3 IR Spectrum of compound **204b**

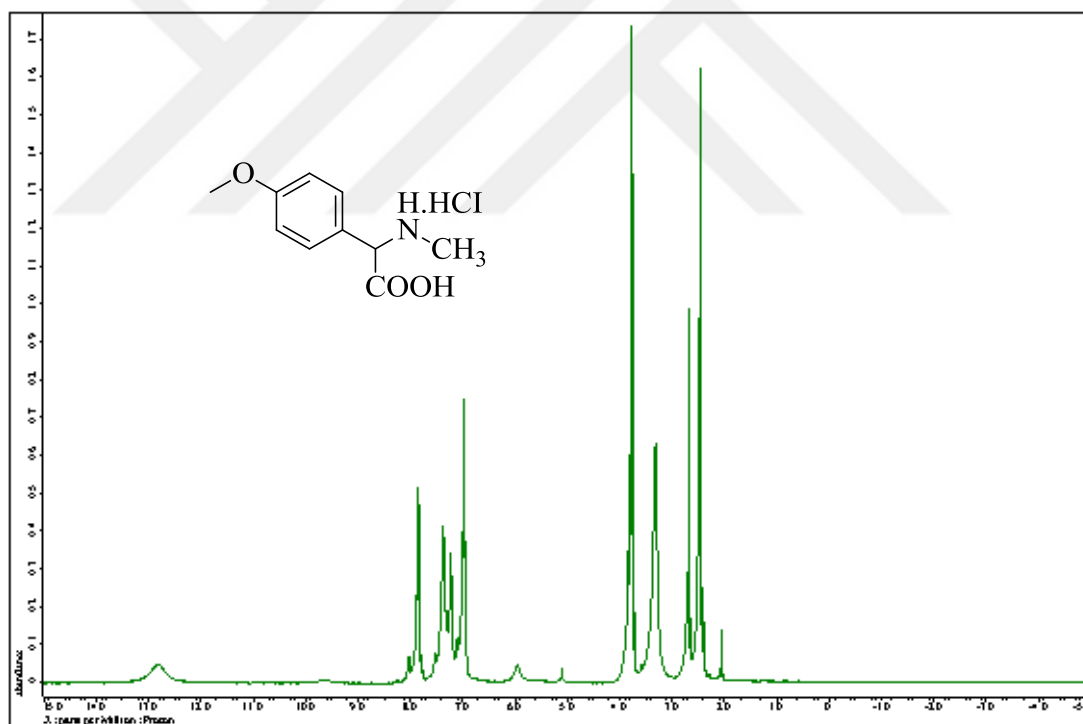


Figure A.4 ¹H NMR Spectrum of compound **204b**

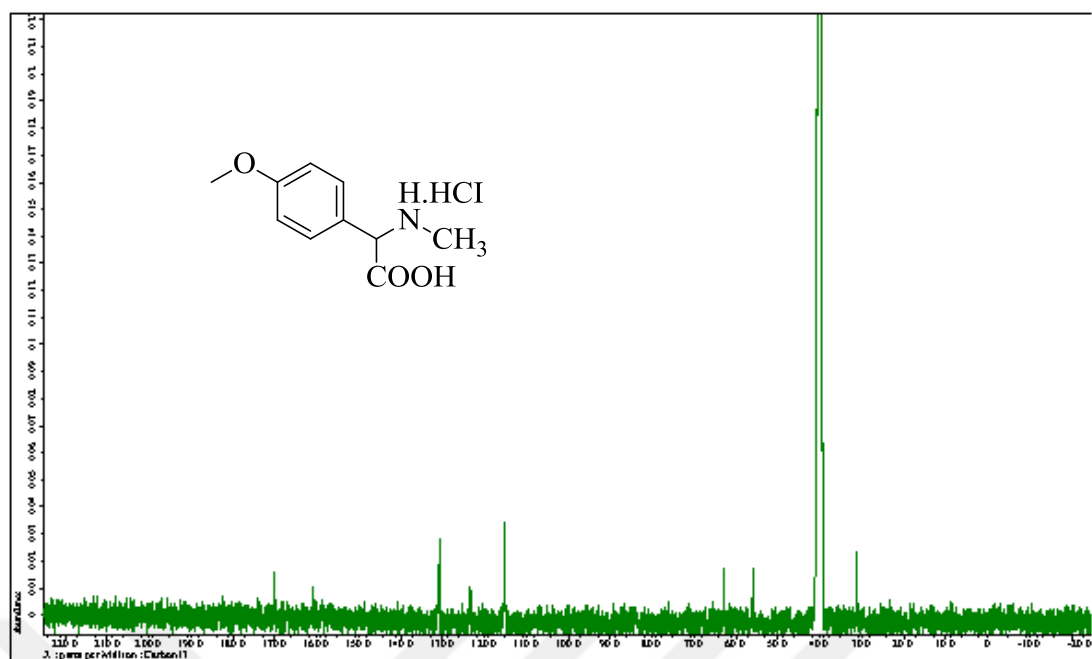


Figure A.5 ^{13}C NMR Spectrum of compound **204b**

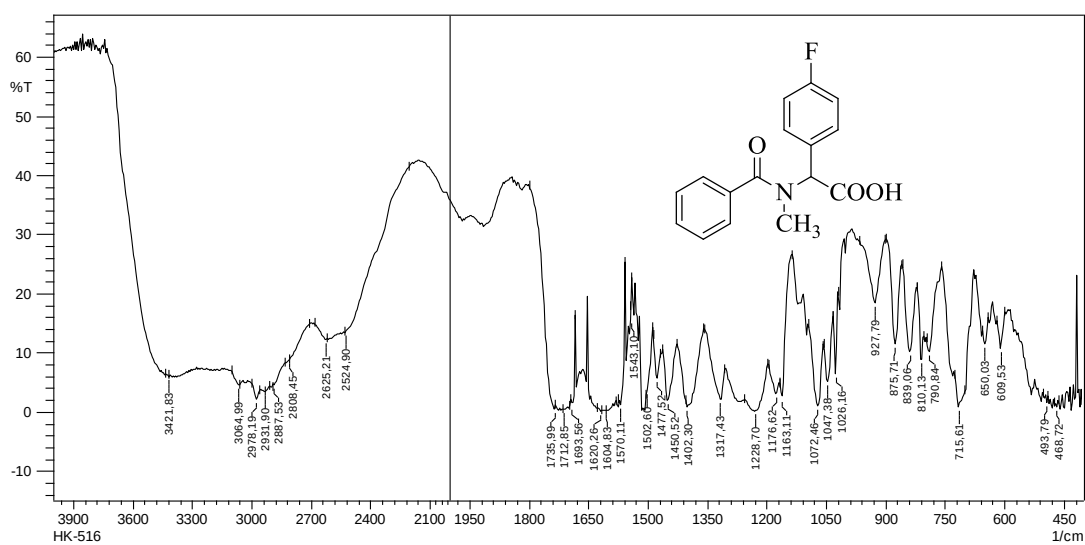


Figure A.6 IR Spectrum of compound **206a**

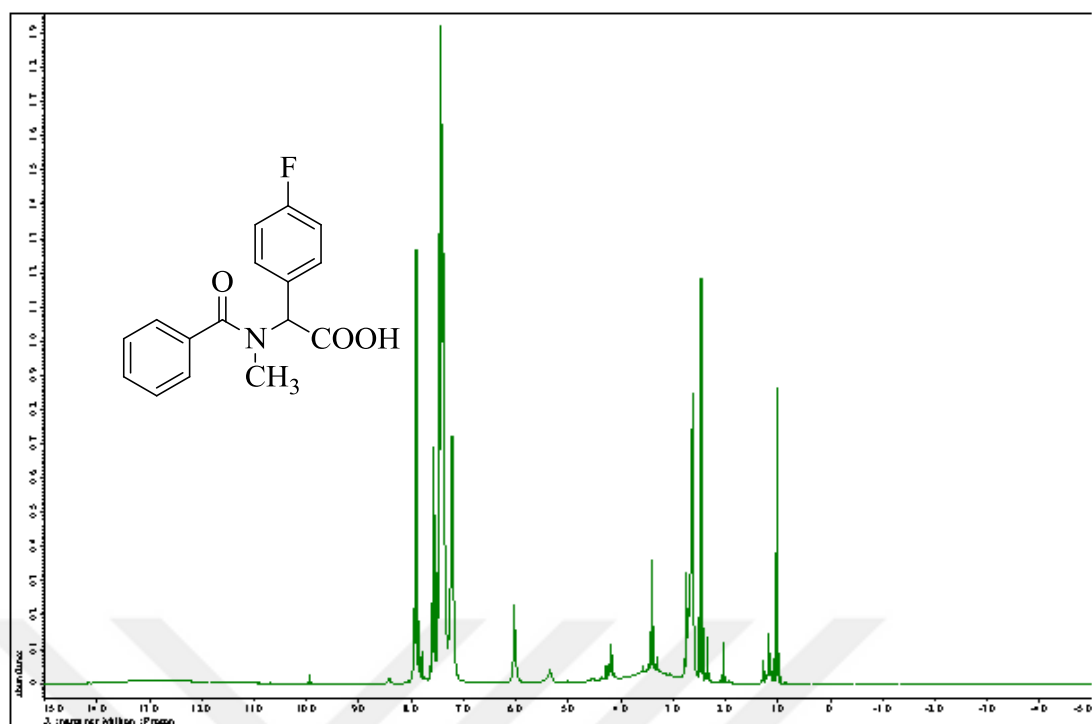


Figure A.7 ^1H NMR Spectrum of compound 206a

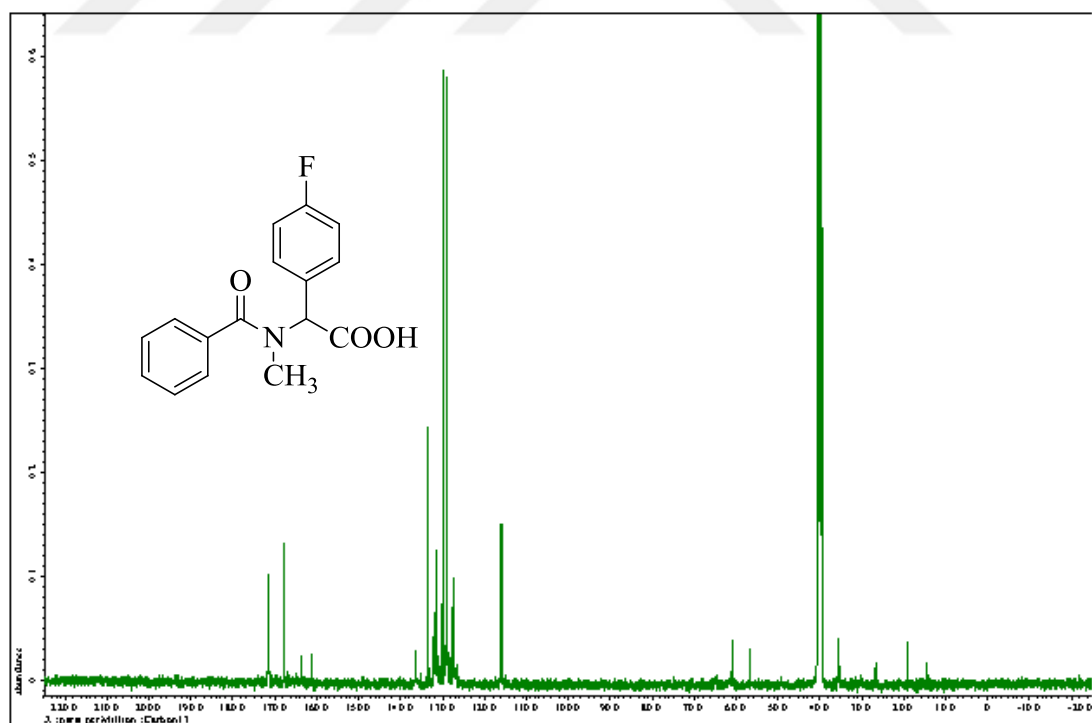


Figure A.8 ^{13}C NMR Spectrum of compound 206

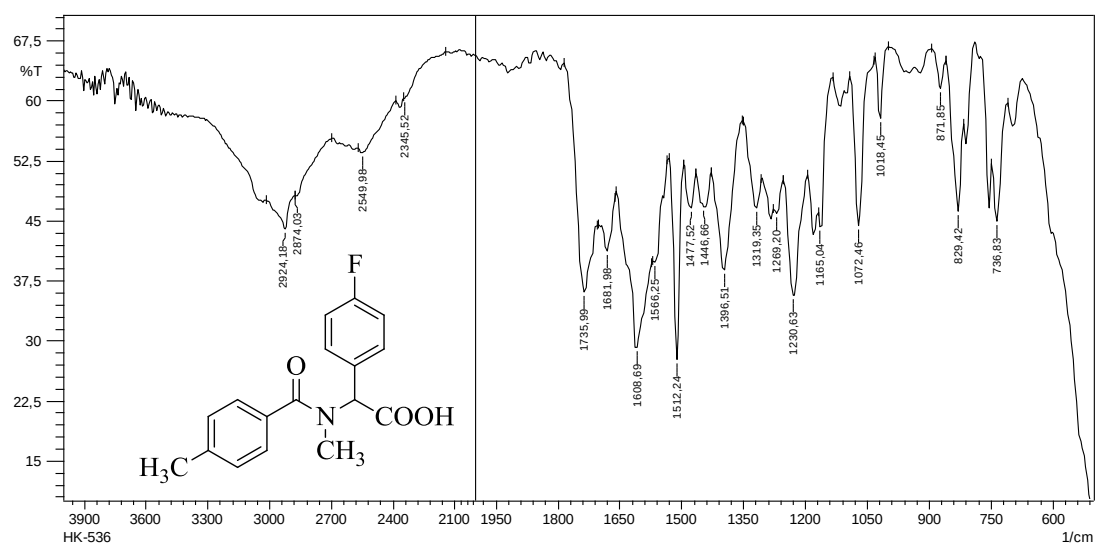
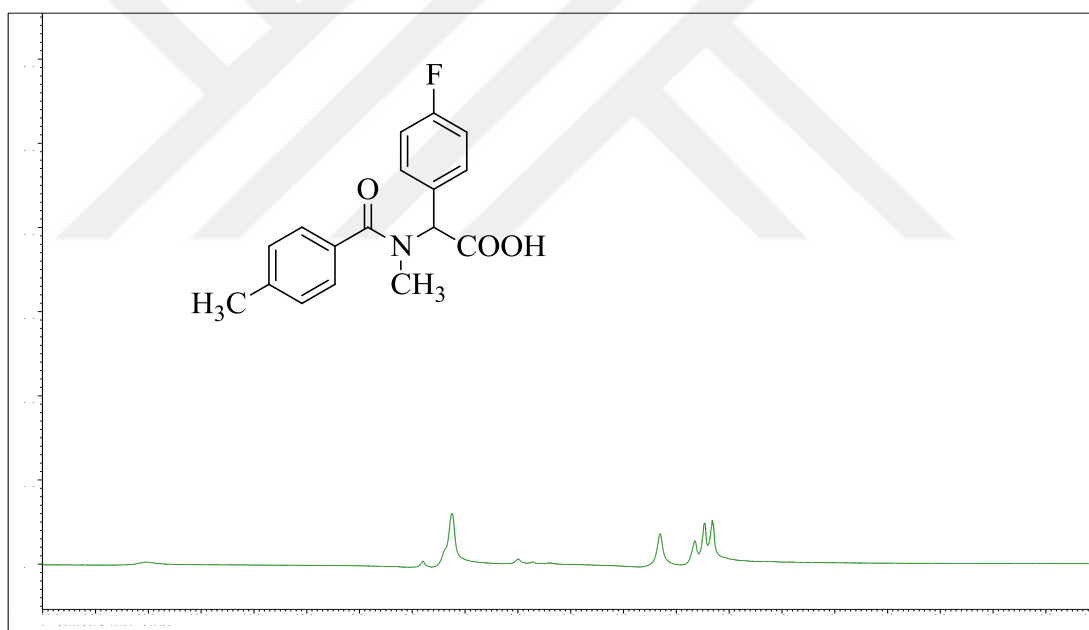


Figure A.9 IR Spectrum of compound **206b**



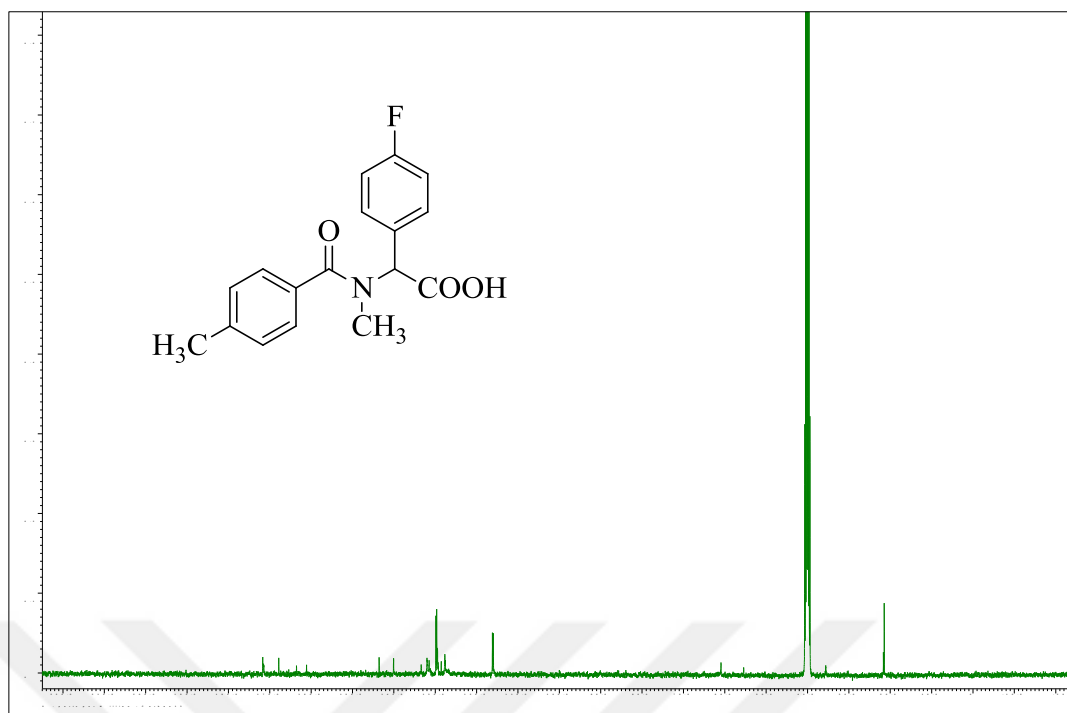


Figure A.11 ¹³C NMR Spectrum of compound **206b**

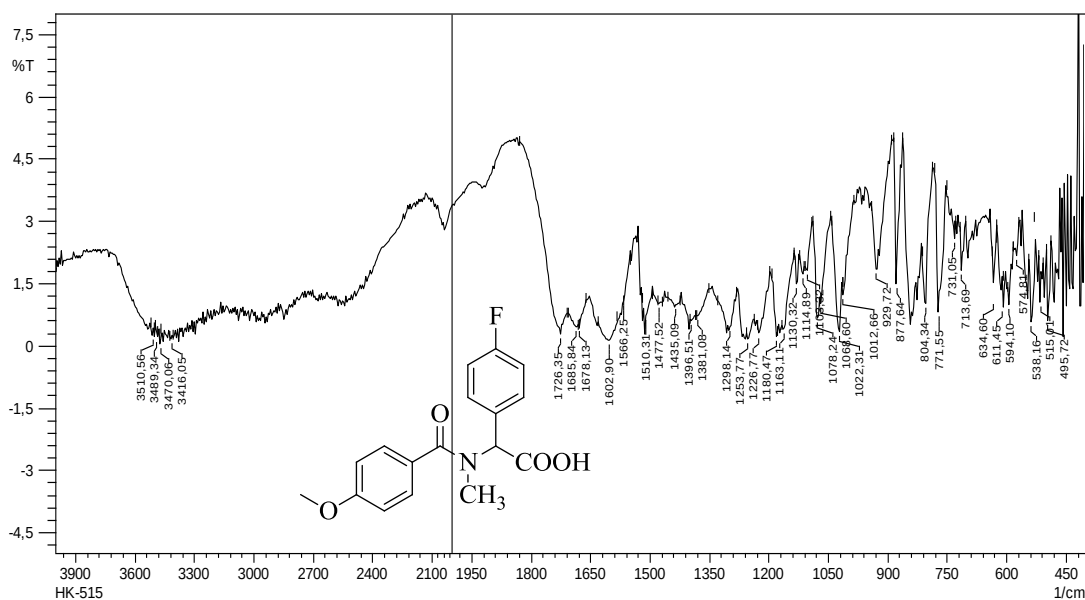


Figure A.12 IR Spectra of compound **206c**

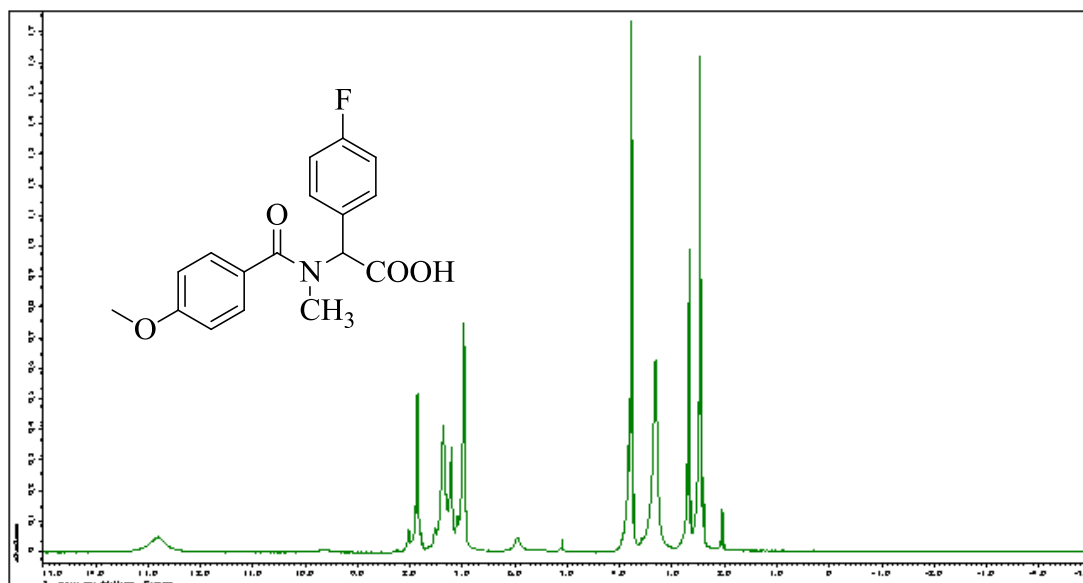


Figure A.13 ¹H NMR Spectrum of compound 206c

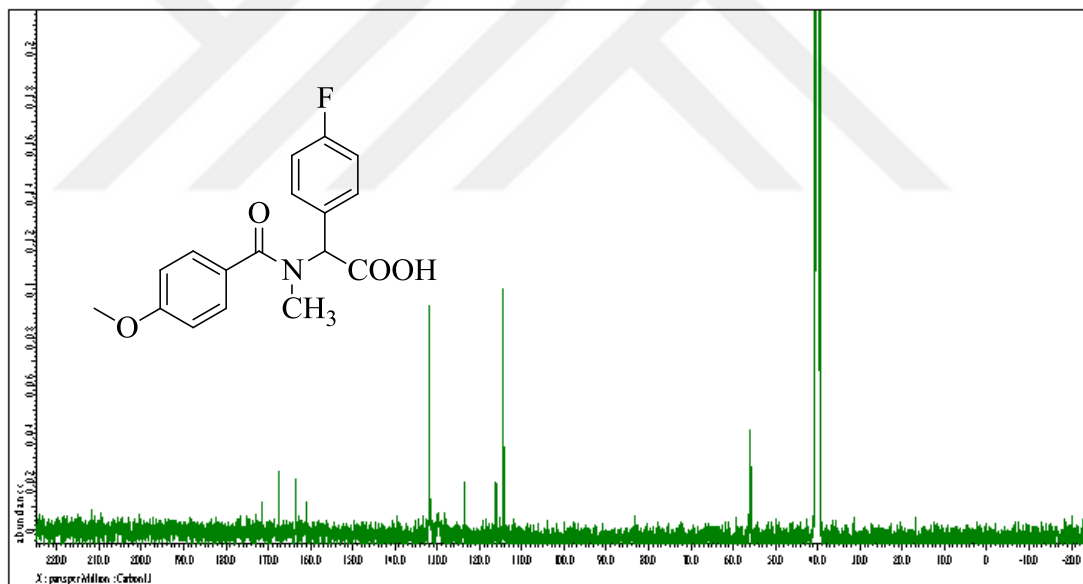


Figure A.14 ¹³C NMR Spectrum of compound 206c

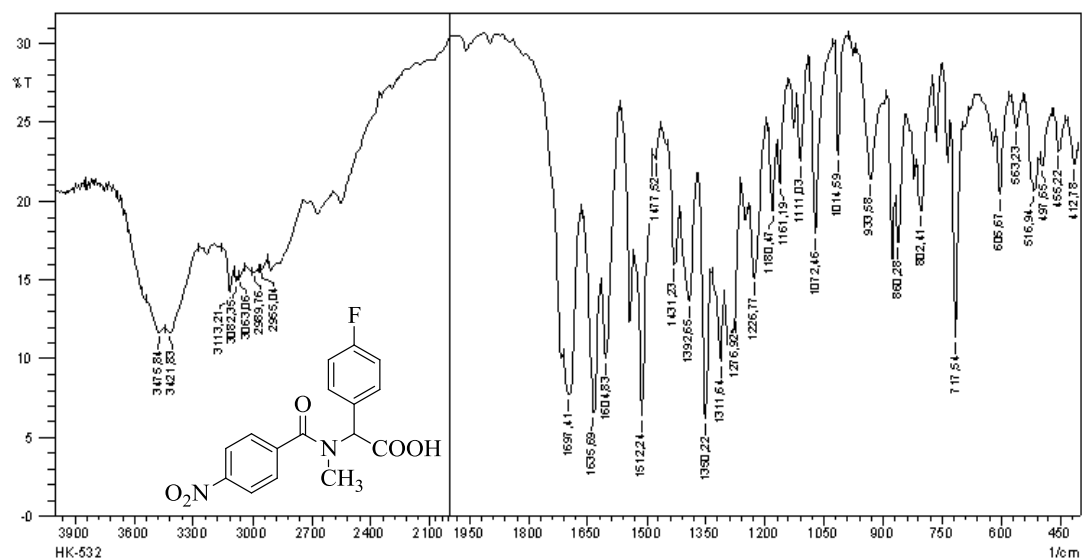


Figure A.15 IR Spectrum of compound **206d**

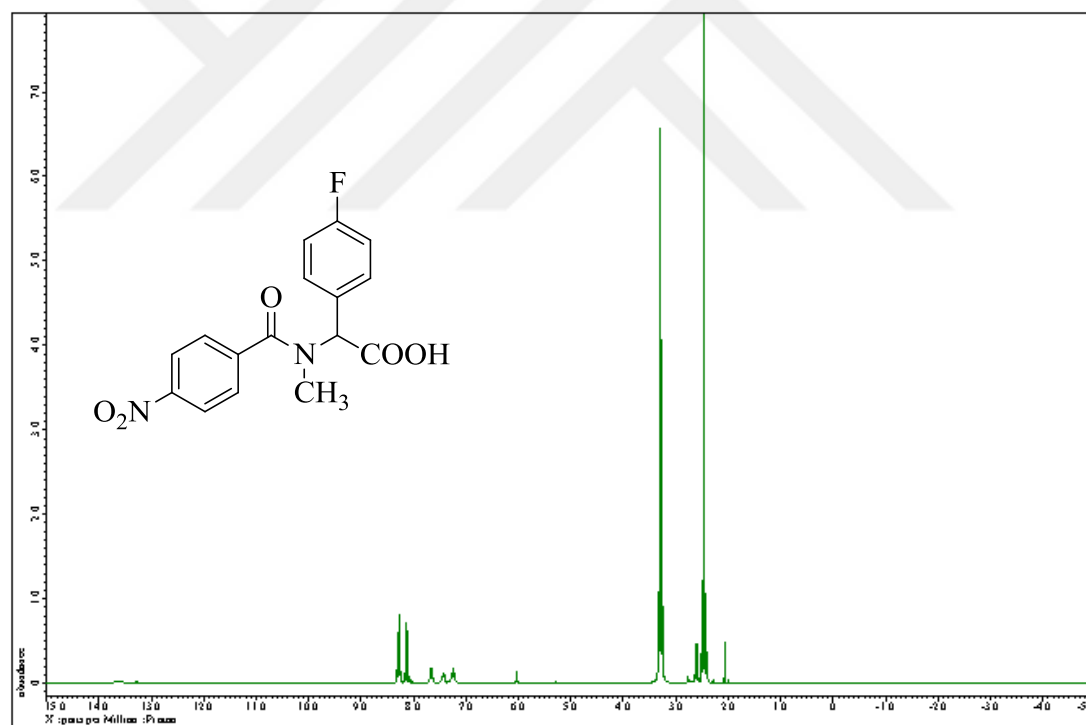


Figure A.16 ¹H NMR Spectrum of compound **206d**

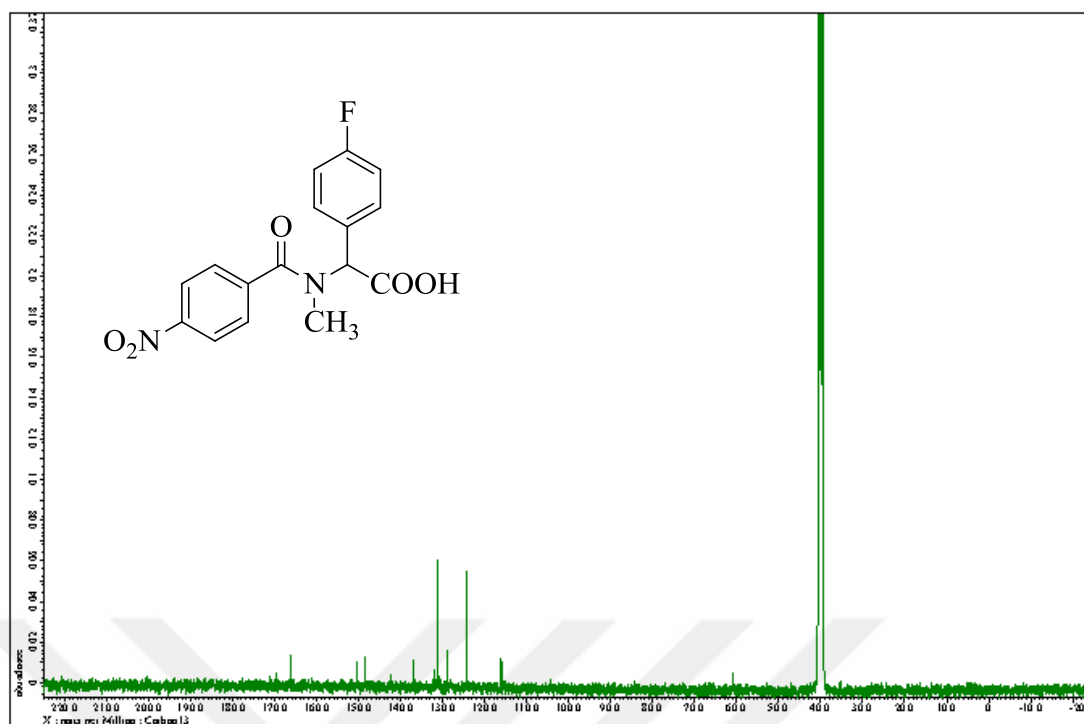


Figure A.17 ¹³C NMR Spectrum of compound 206d

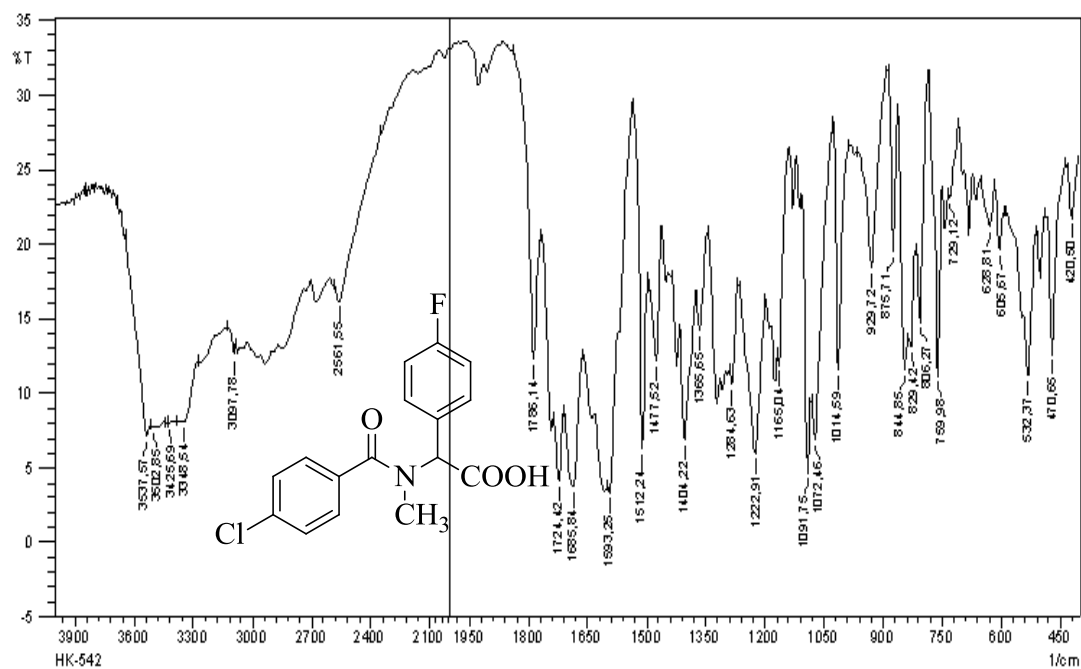


Figure A.18 IR Spectrum of compound 206e

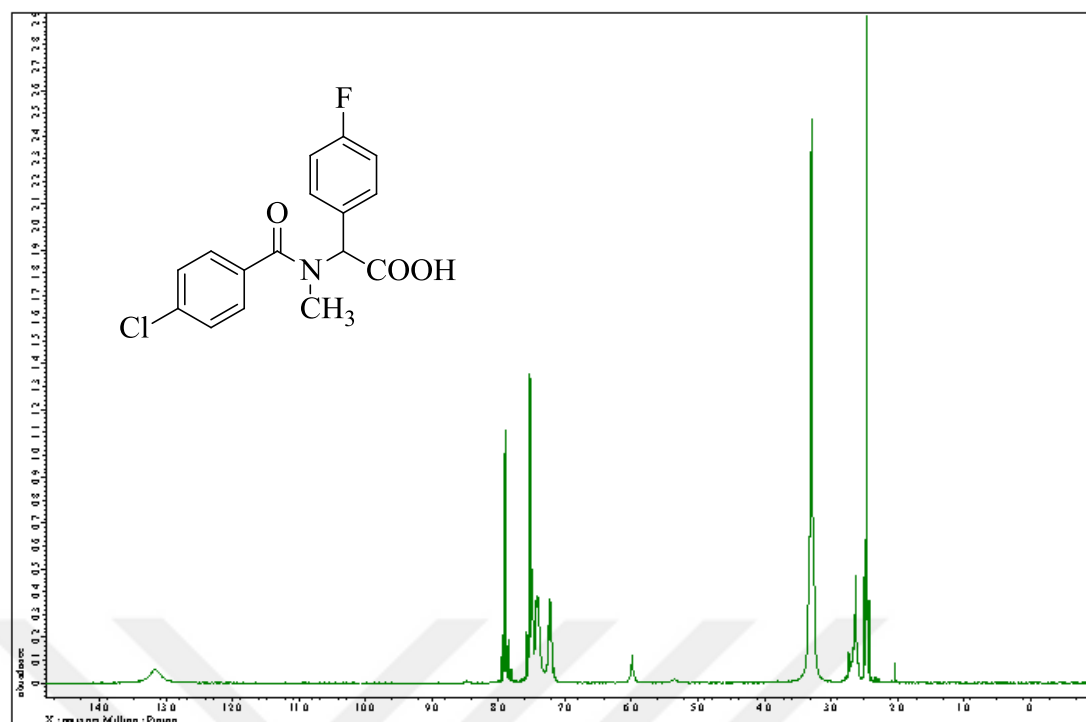


Figure A.19 ¹H NMR Spectrum of compound 206e

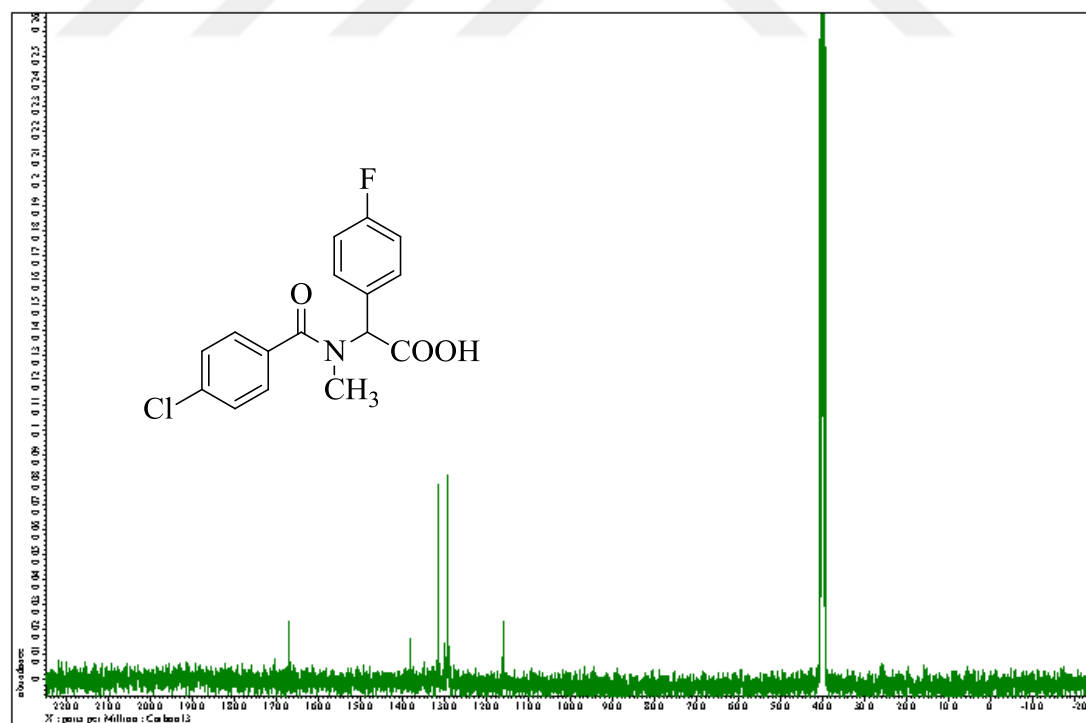


Figure A.20 ¹³C NMR Spectrum of compound 206e

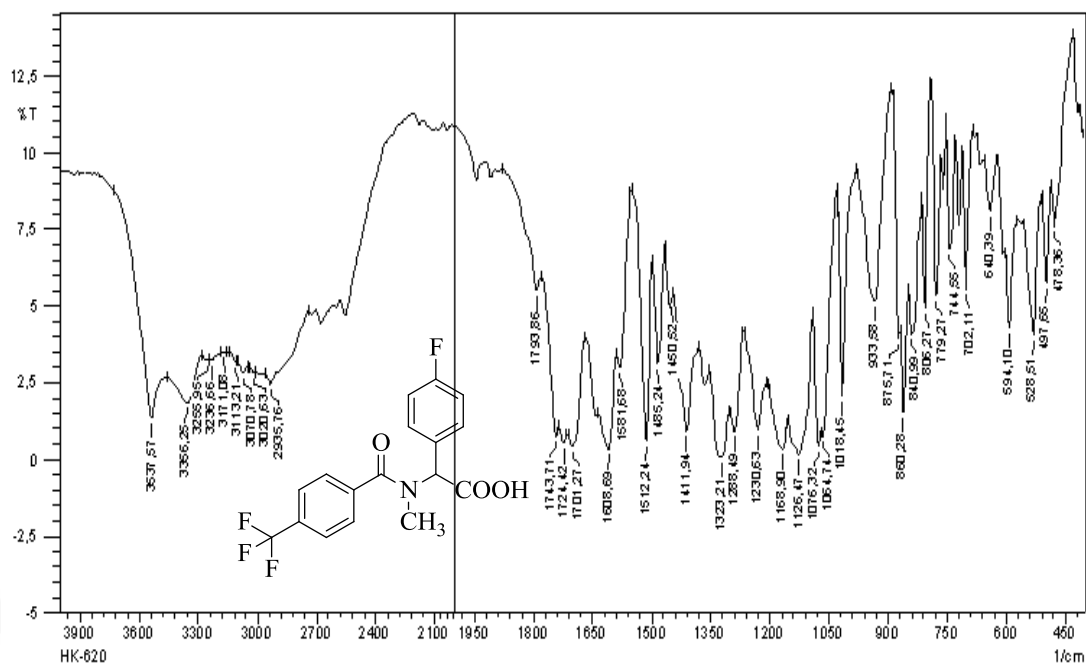


Figure A.21 IR Spectrum of compound **206f**

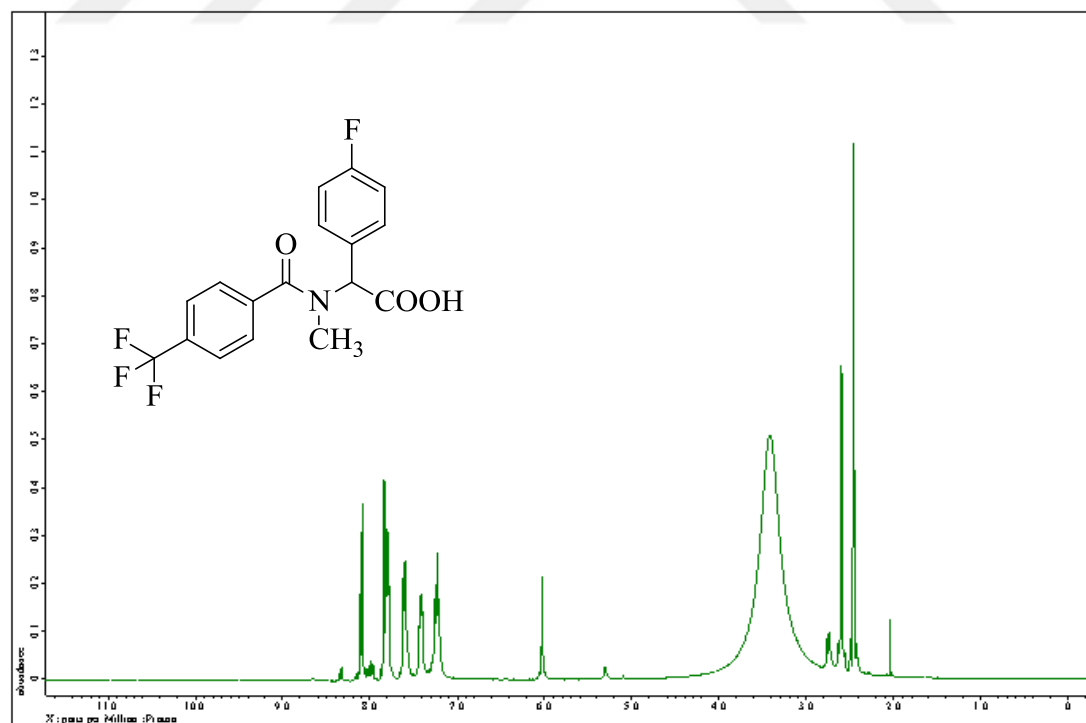


Figure A.22 ^1H NMR Spectrum of compound **206f**

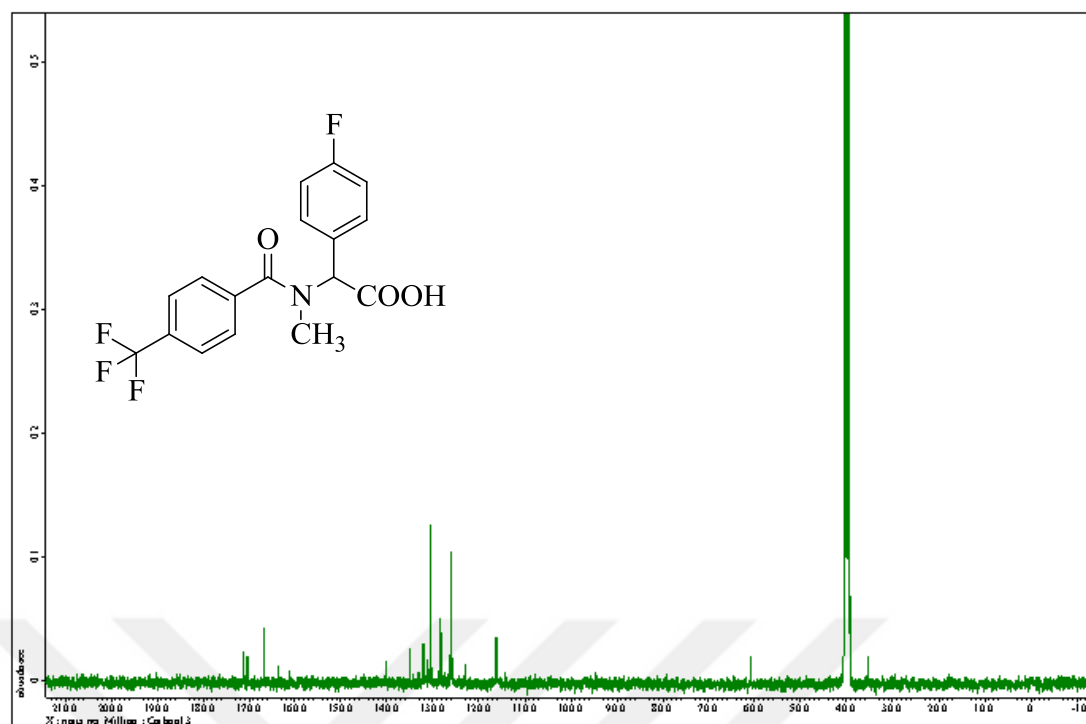


Figure A.23 ¹³C NMR Spectrum of compound 206f

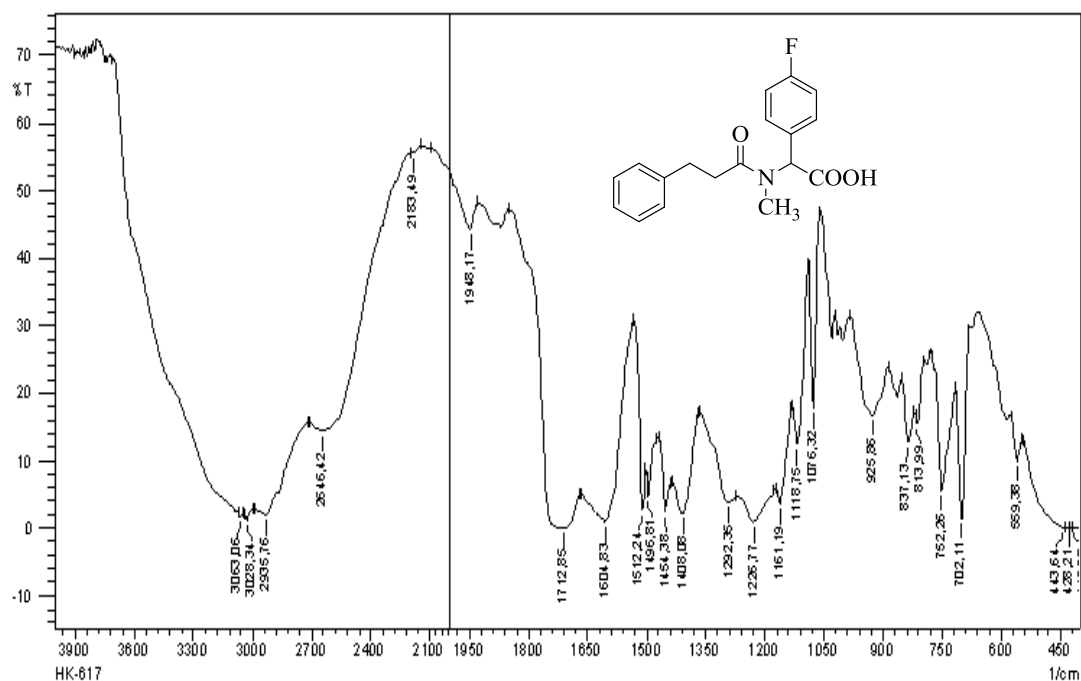


Figure A.24 IR Spectrum of compound 206g

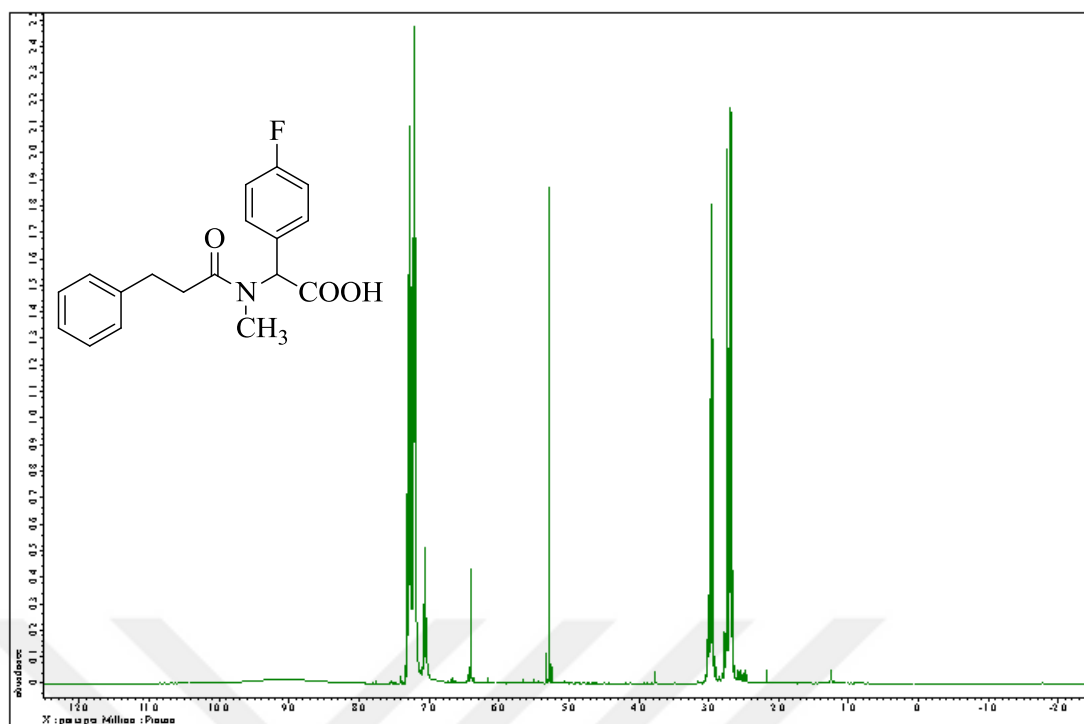


Figure A.25 ¹H NMR Spectrum of compound **206g**

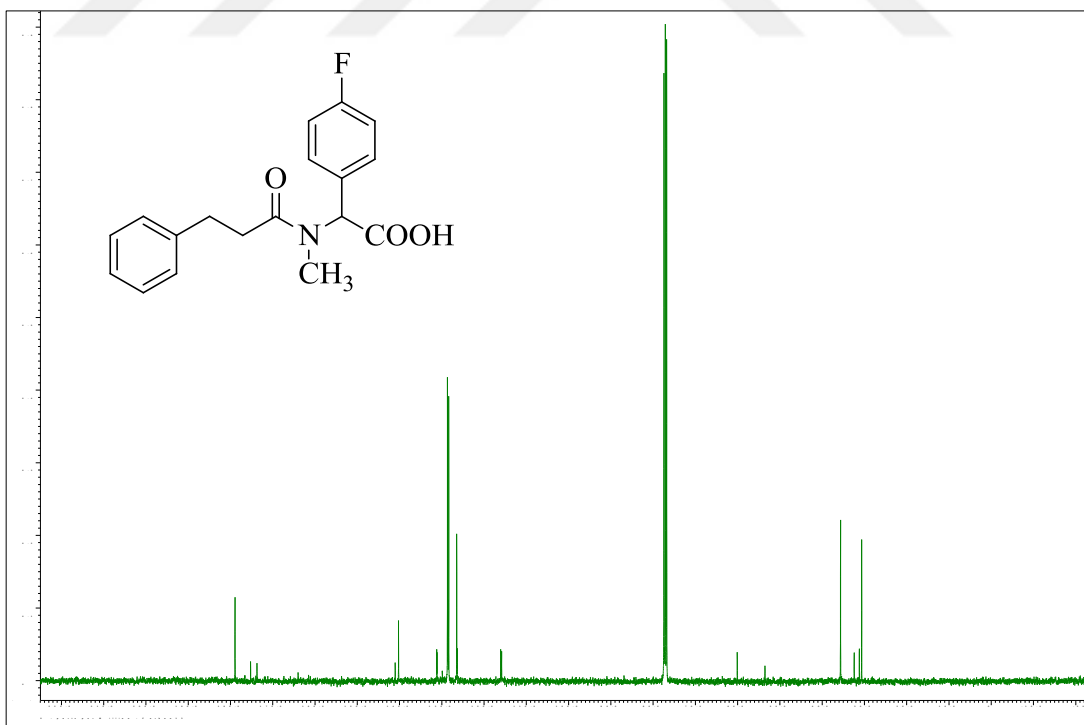


Figure A.26 ¹³C NMR Spectrum of compound **206g**

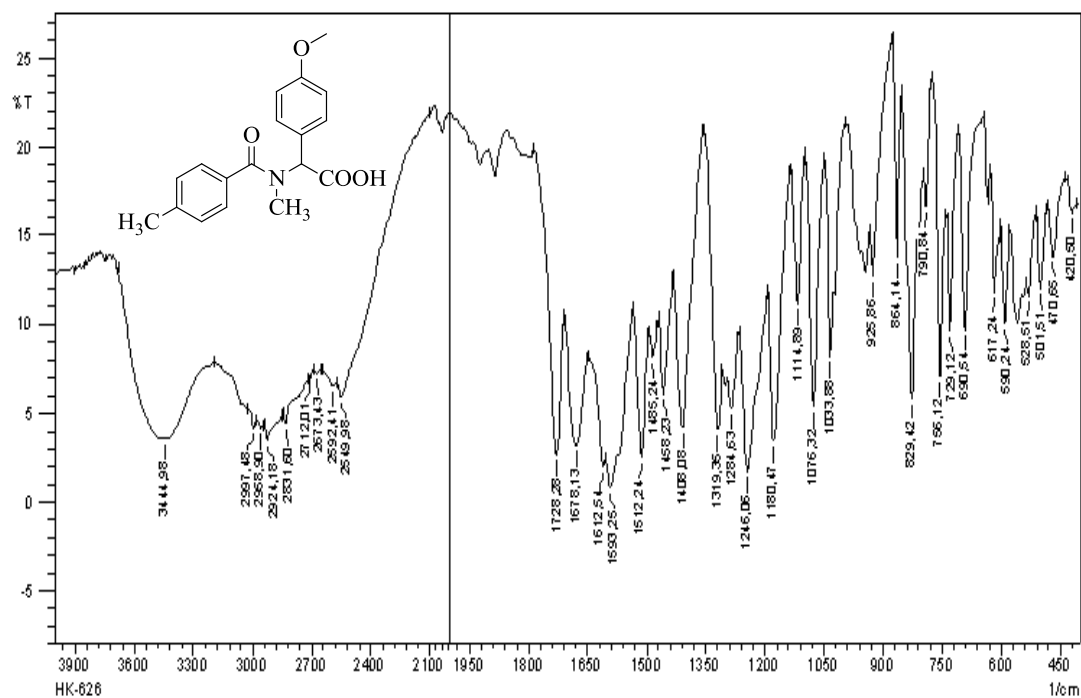


Figure A.27 IR Spectrum of compound 206h

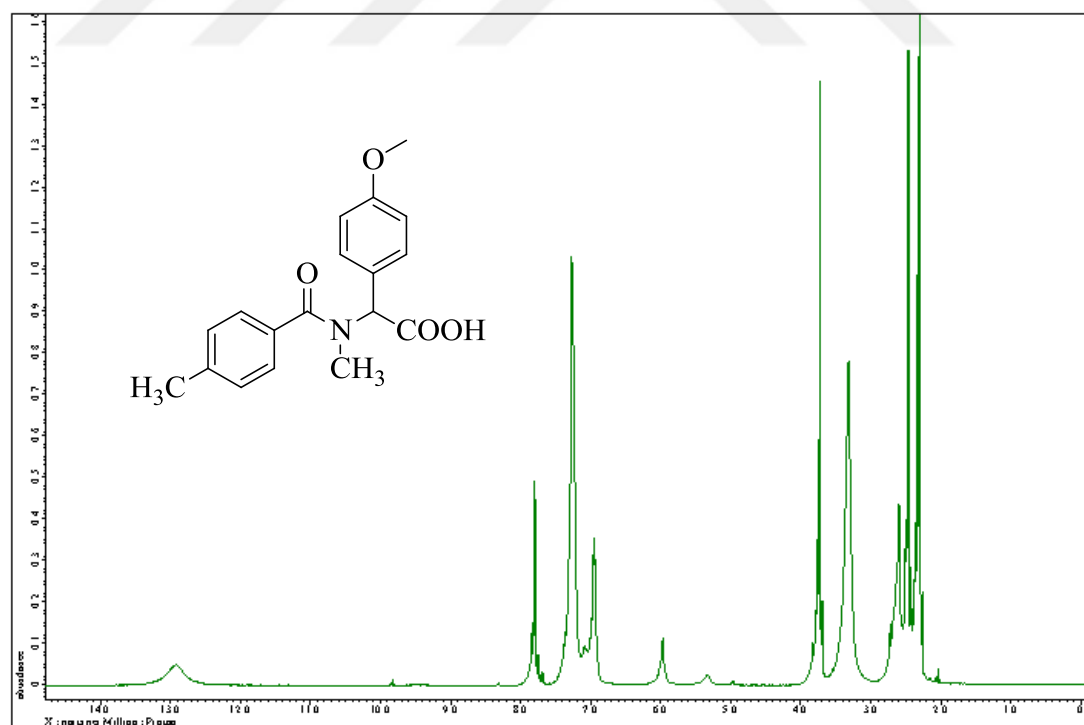


Figure A.28 ¹H NMR Spectrum of compound 206h

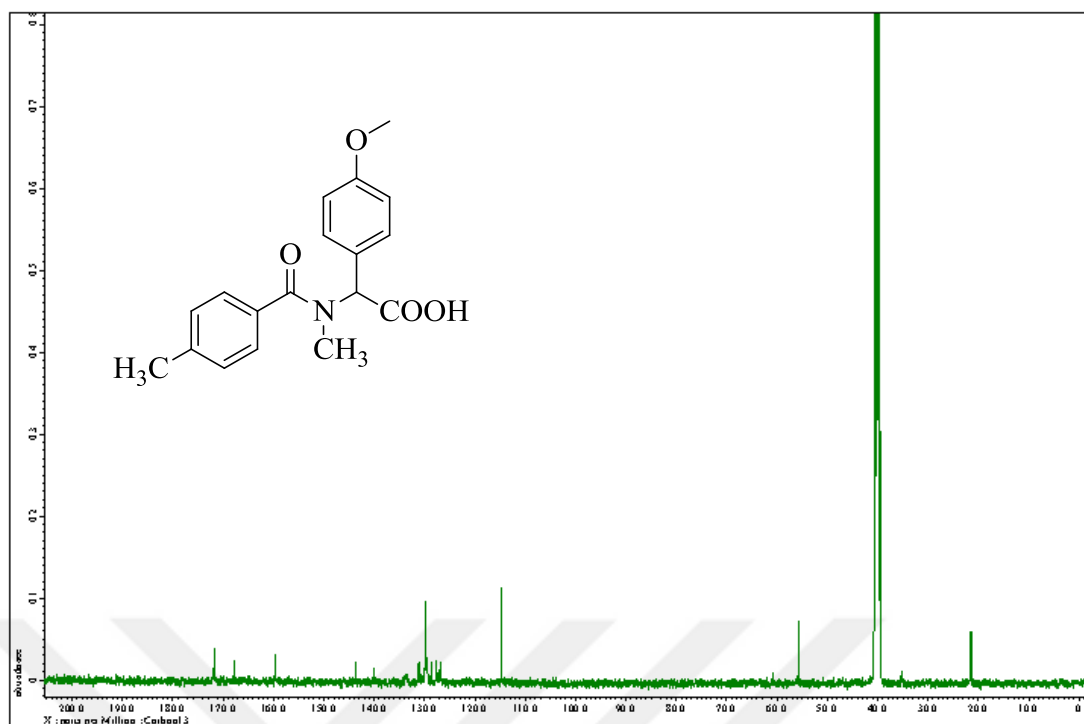


Figure A.29 ¹³C NMR Spectrum of compound 206h

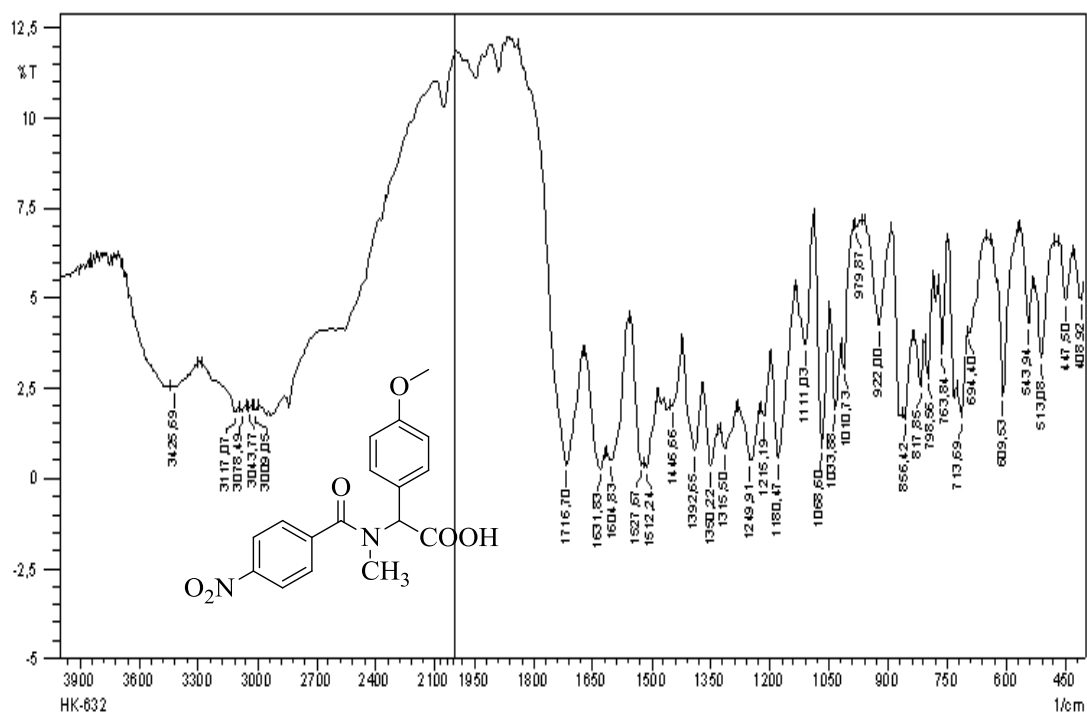


Figure A.30 IR Spectrum of compound 206i

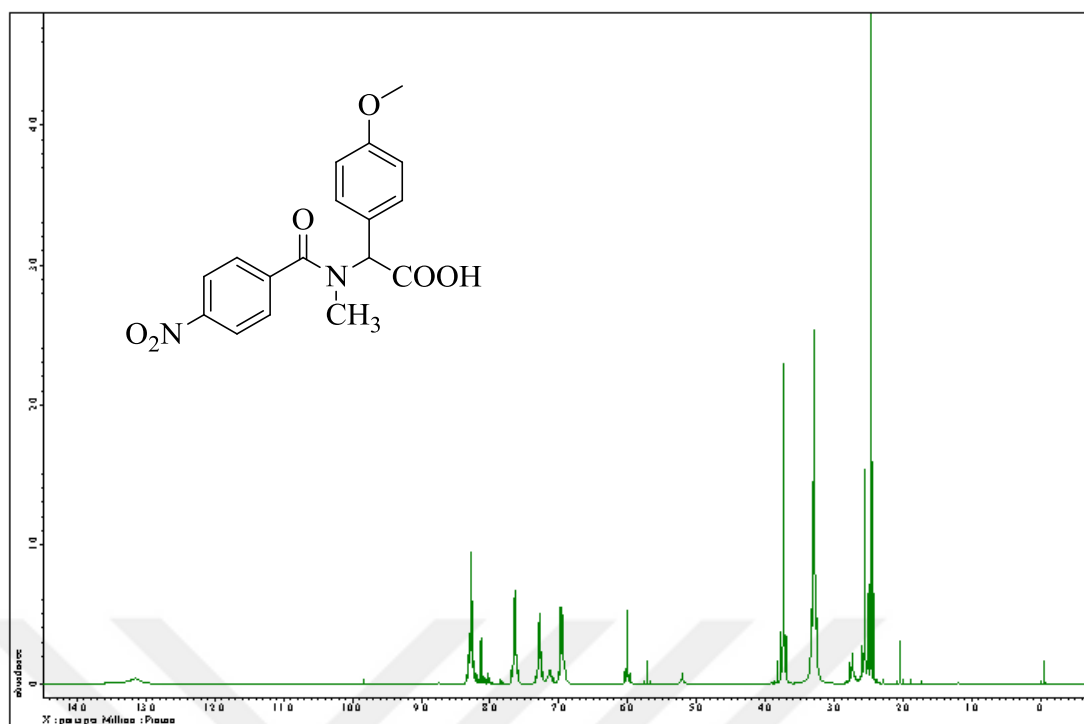


Figure A.31 ¹H NMR Spectrum of compound 206i

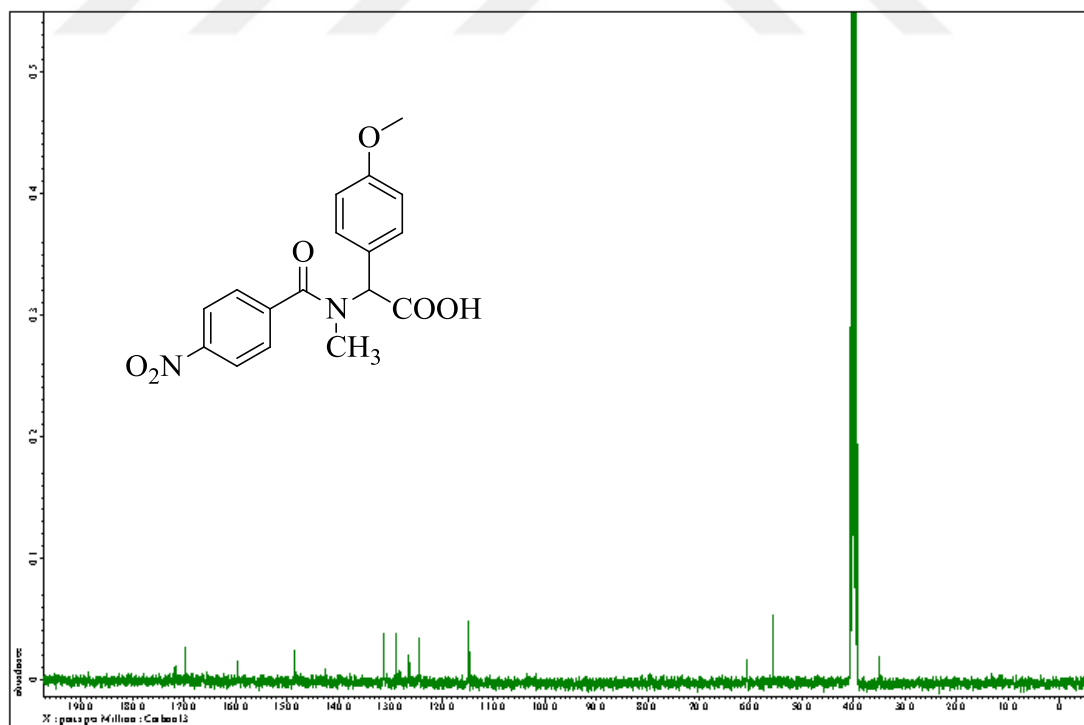


Figure A.32 ¹³C NMR Spectrum of compound 206i

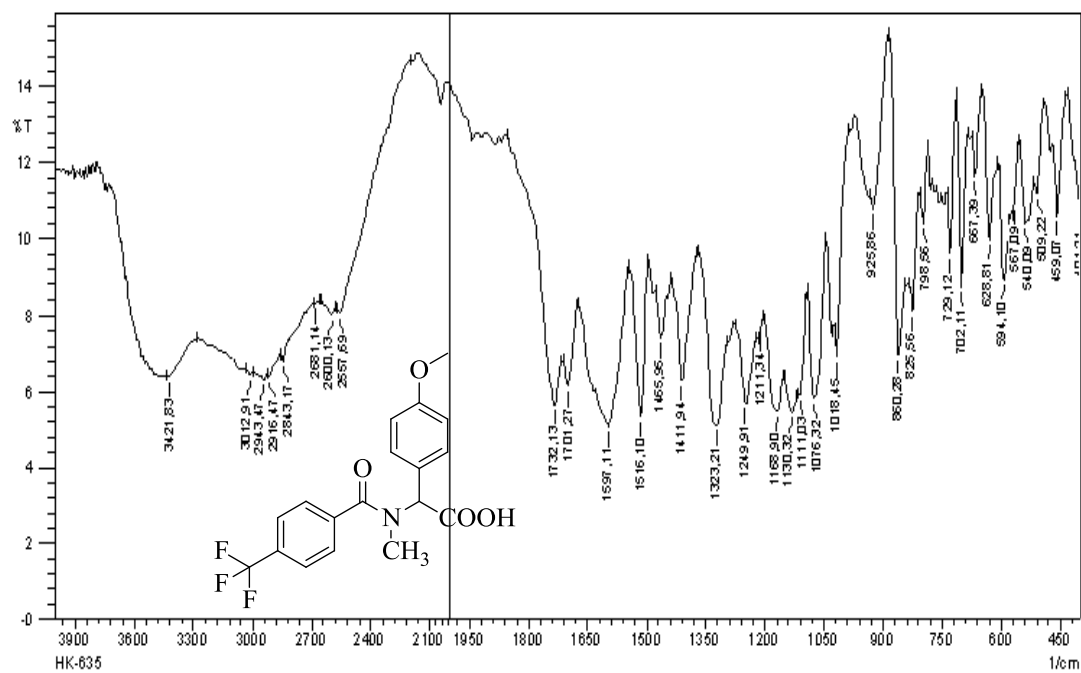


Figure A.33 IR Spectrum of compound 206j

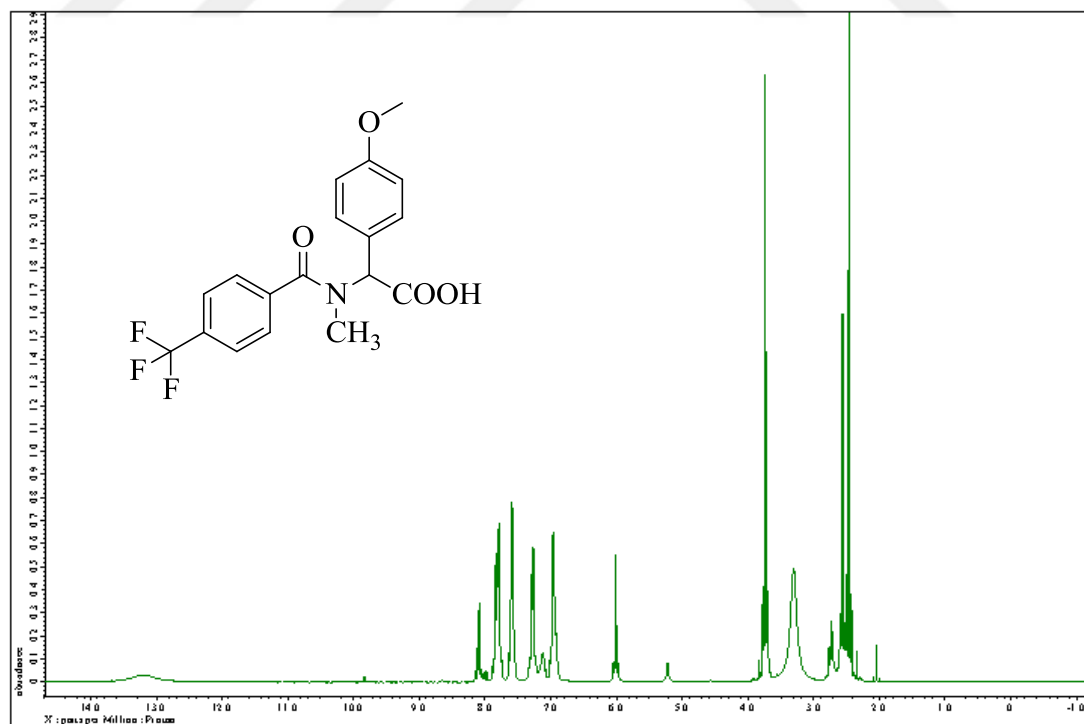


Figure A.34 ¹H NMR Spectrum of compound 206j

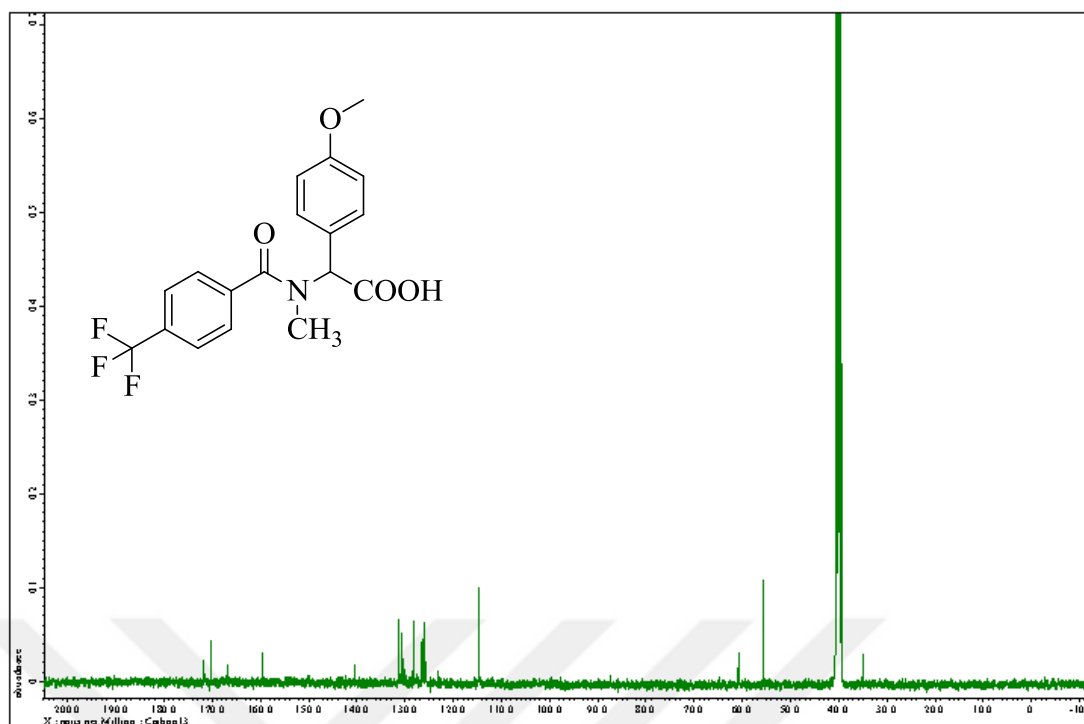


Figure A.35 ¹³C NMR Spectrum of compound 206j

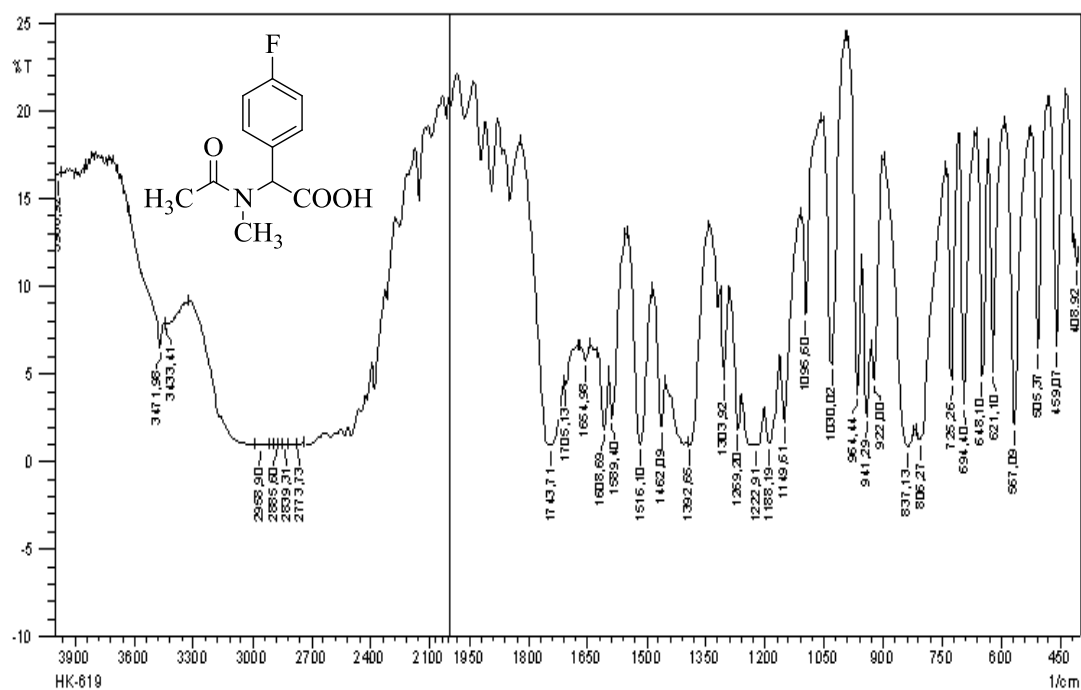


Figure A.36 IR Spectrum of compound 206k

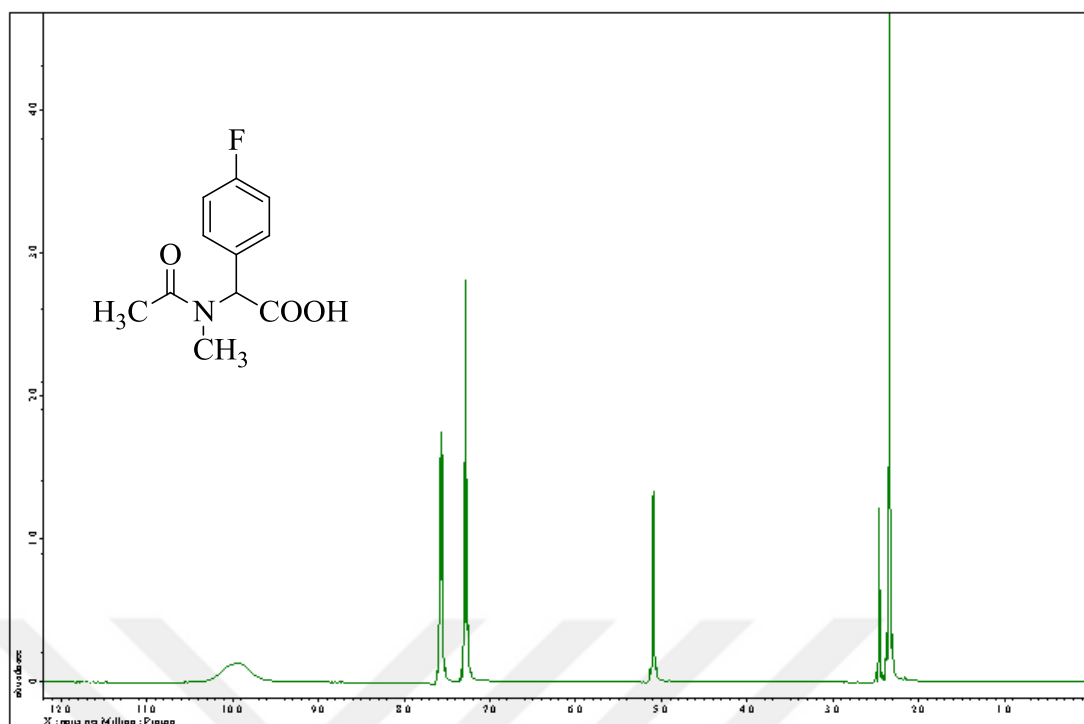


Figure A.37 ¹H NMR Spectrum of compound **206k**

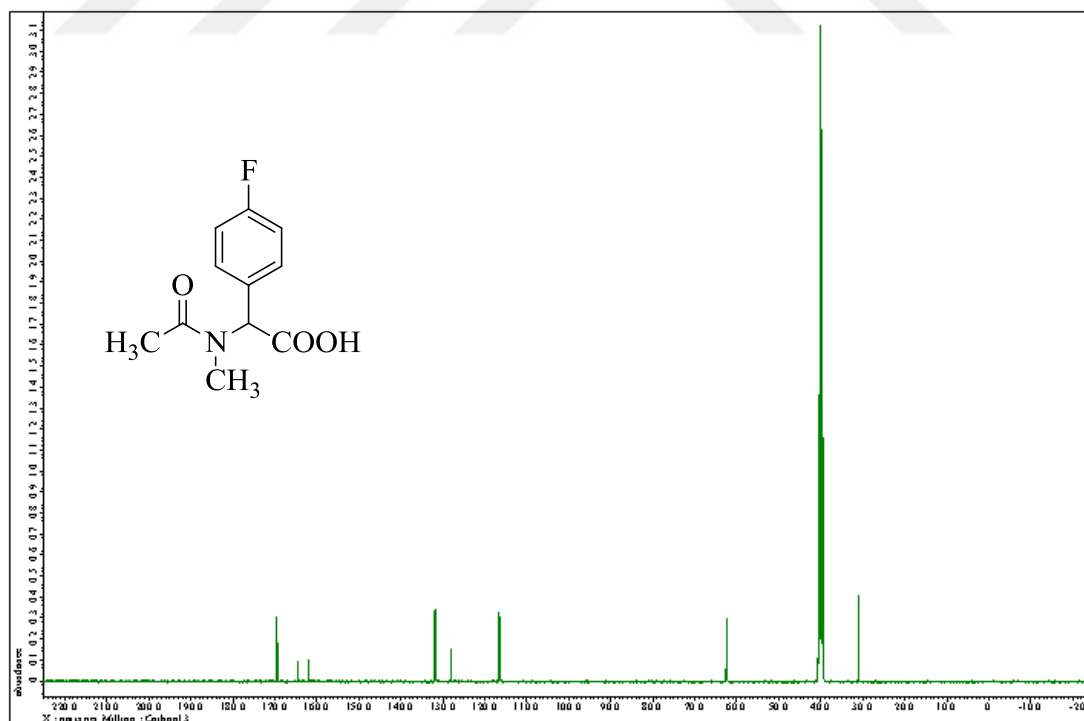


Figure A.38 ¹³C NMR Spectrum of compound **206k**

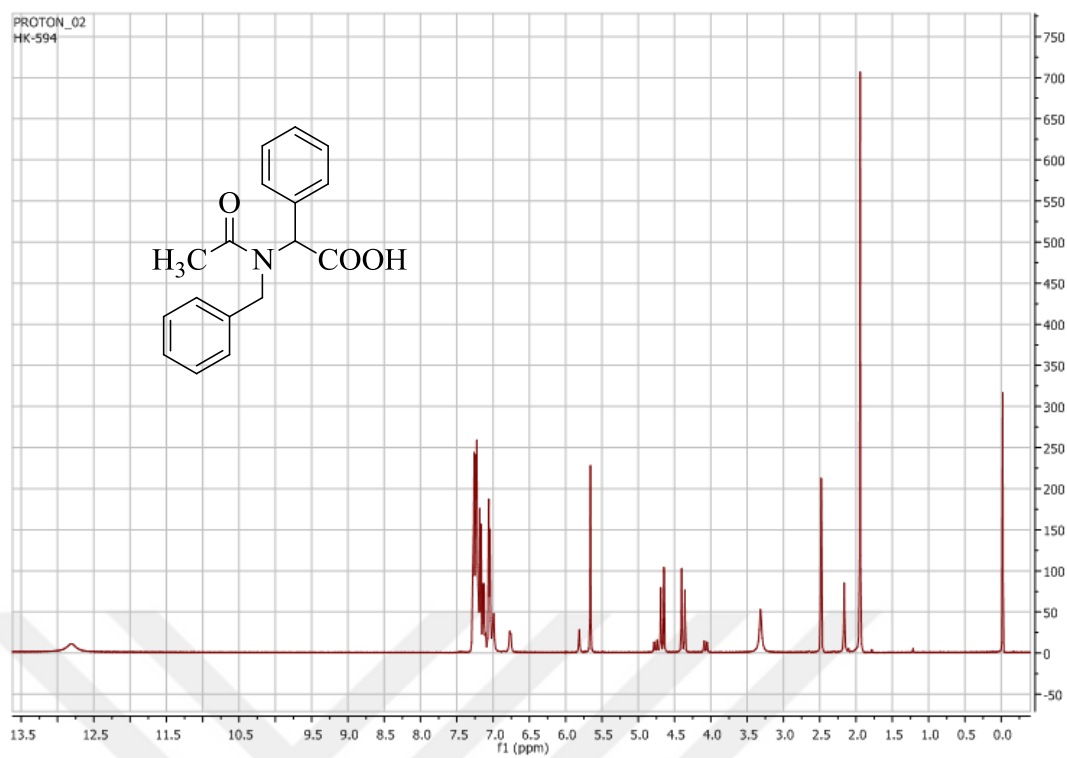


Figure A.39 ¹H NMR Spectrum of compound **206I**

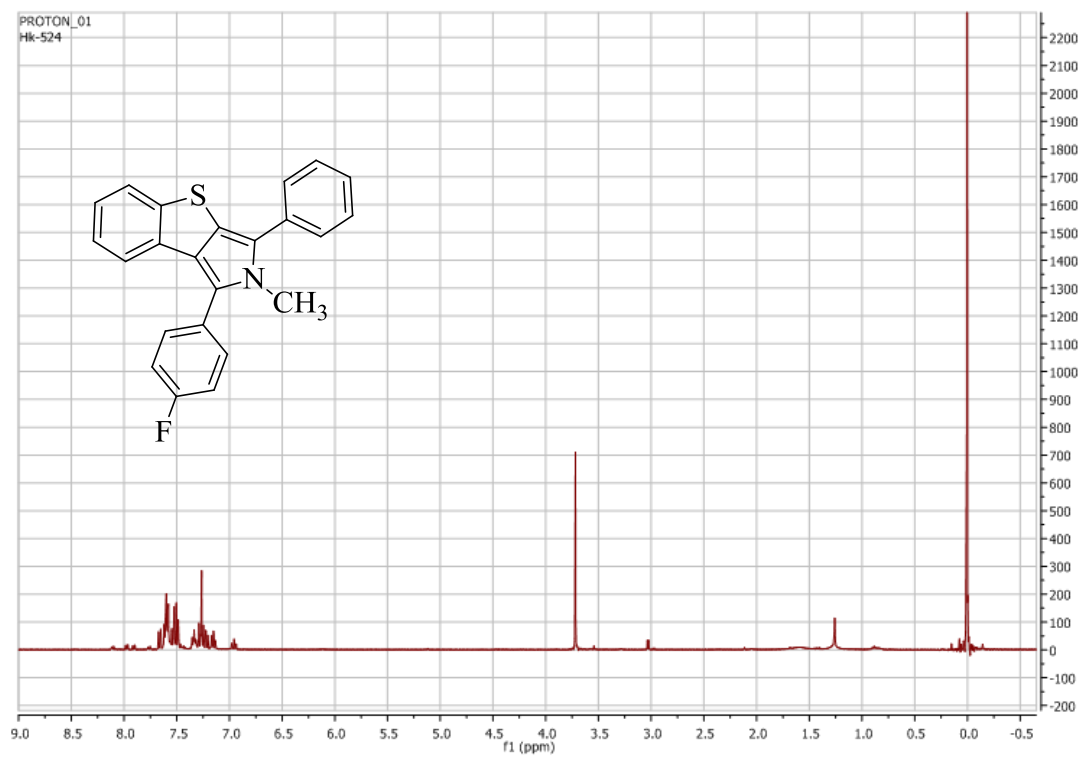


Figure A.40 ¹H NMR Spectrum of compound **207a**

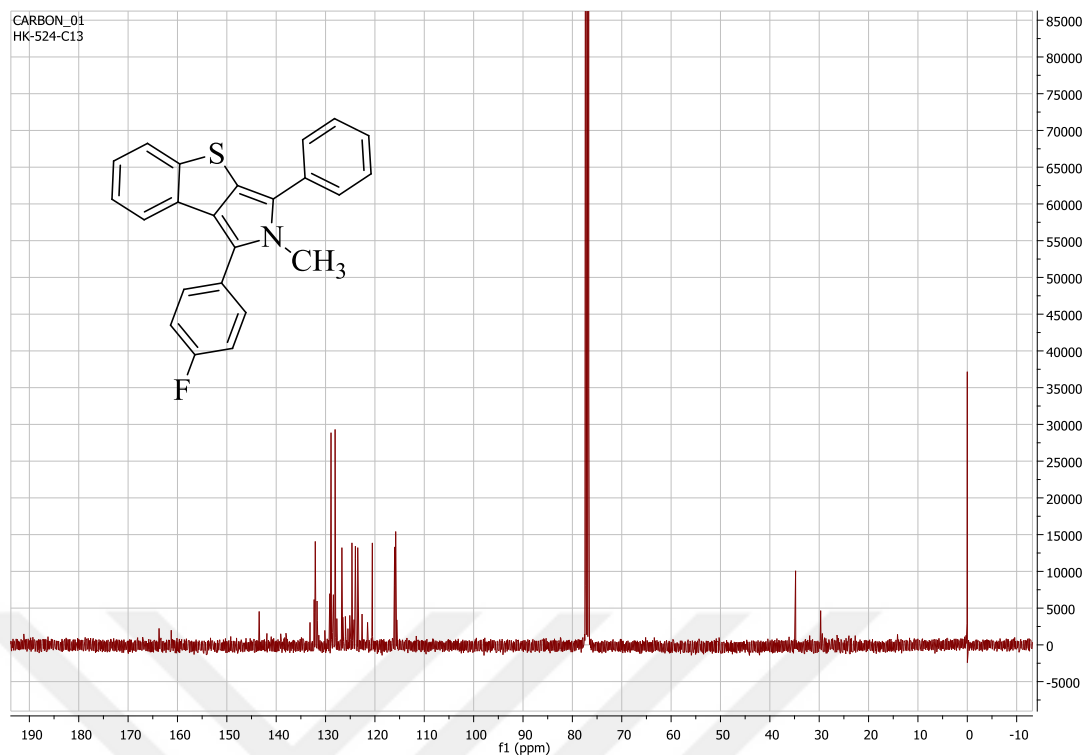


Figure A.41 ^{13}C NMR Spectrum of compound **207a**

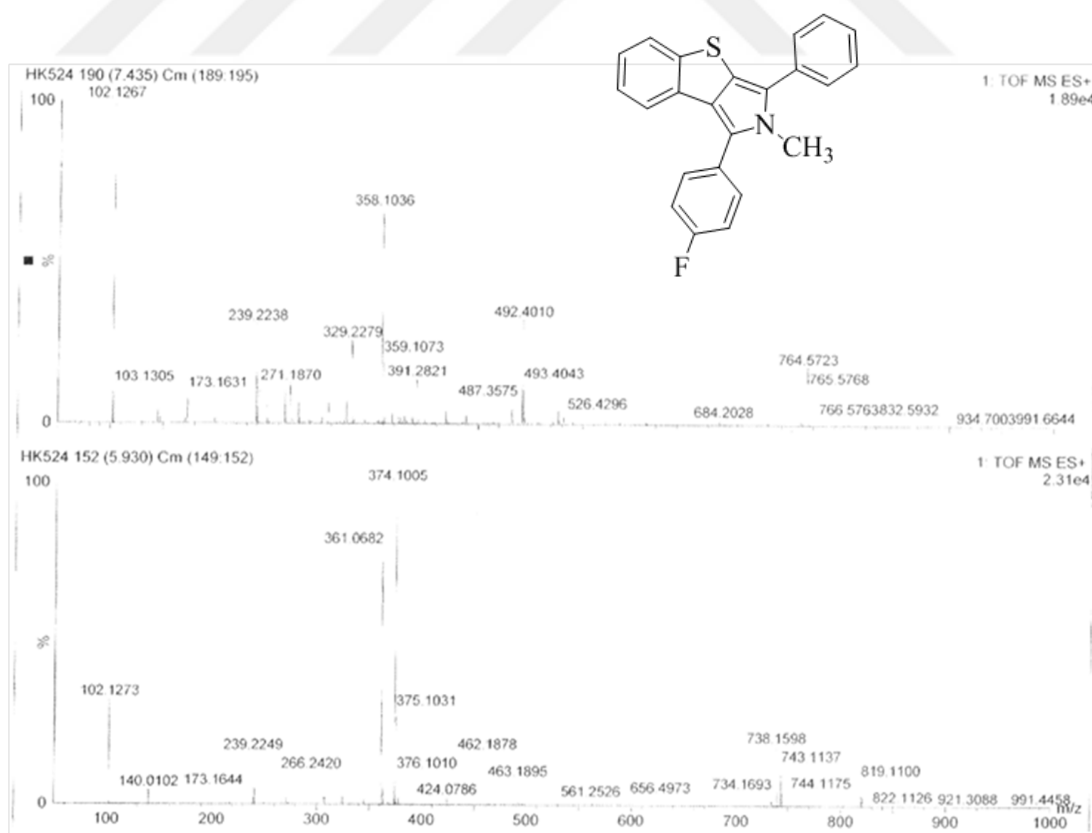


Figure A.42 MASS Spectrum of compound **207a**

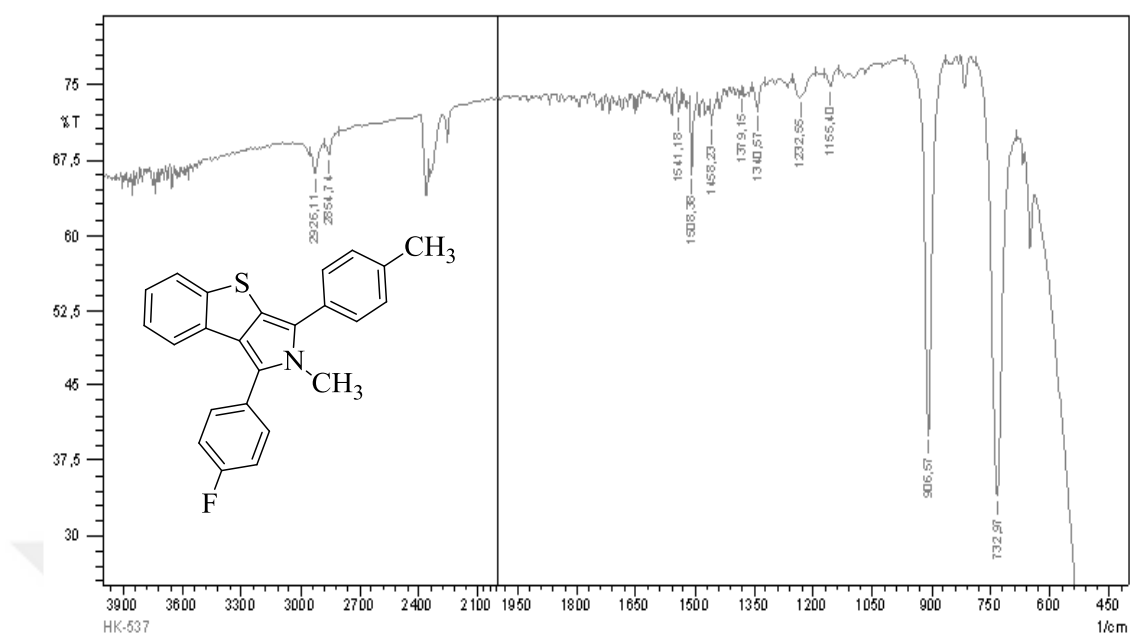


Figure A.43 IR Spectra of compound **207b**

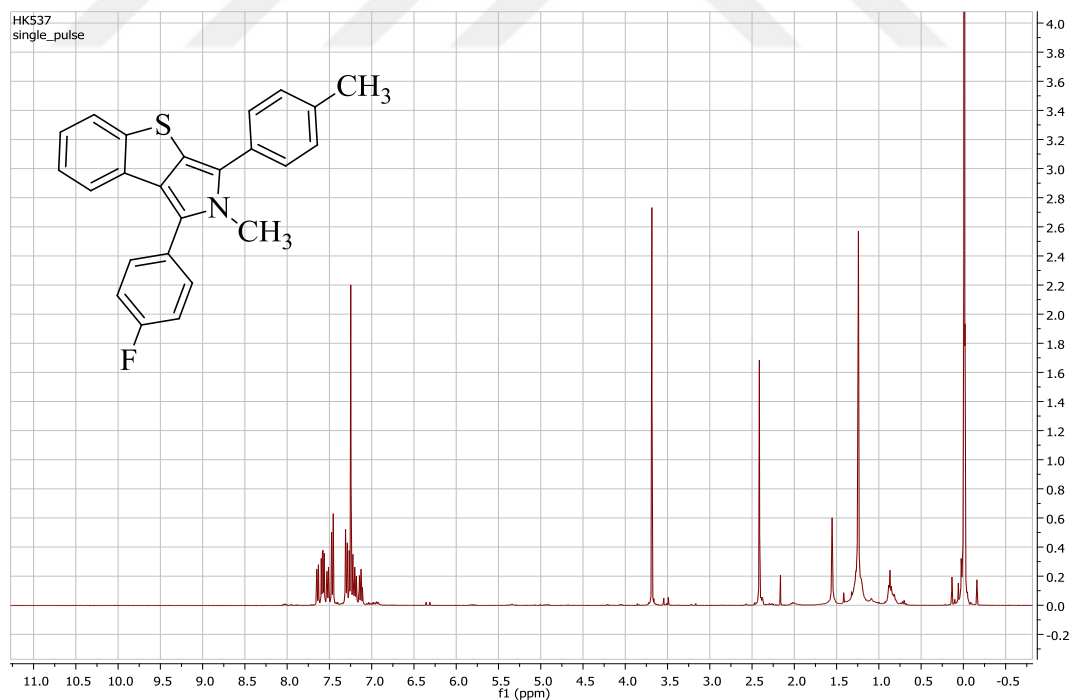


Figure A.44 ^1H NMR Spectrum of compound **207b**

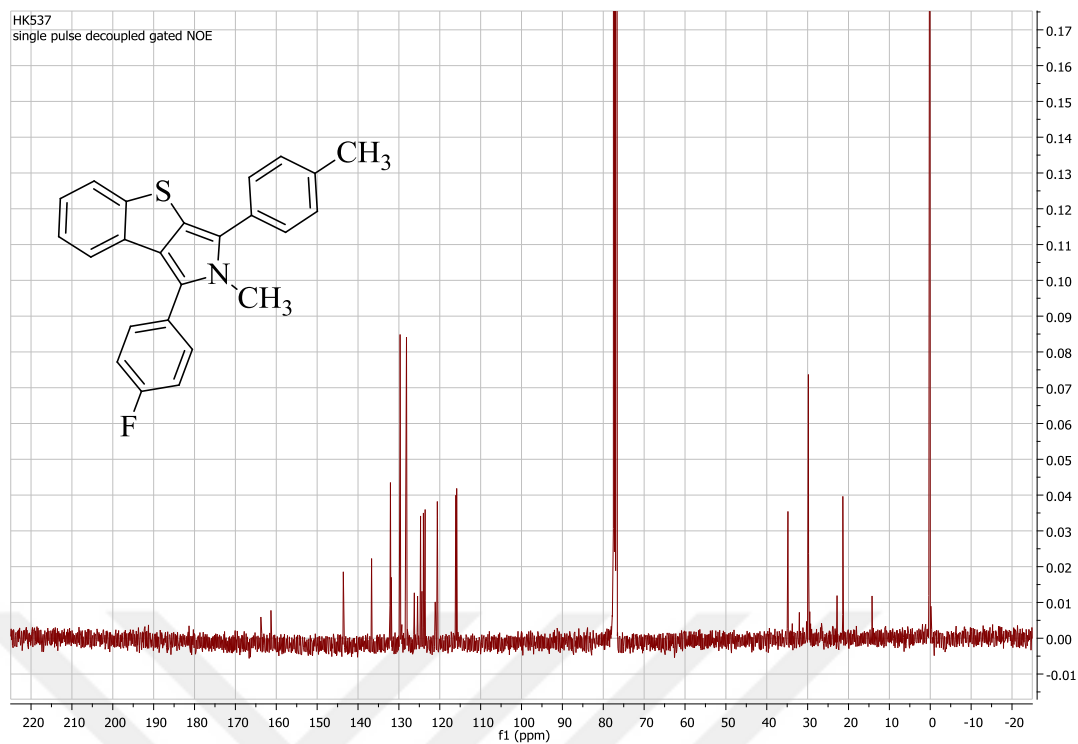


Figure A.45 ^{13}C NMR Spectrum of compound 207b

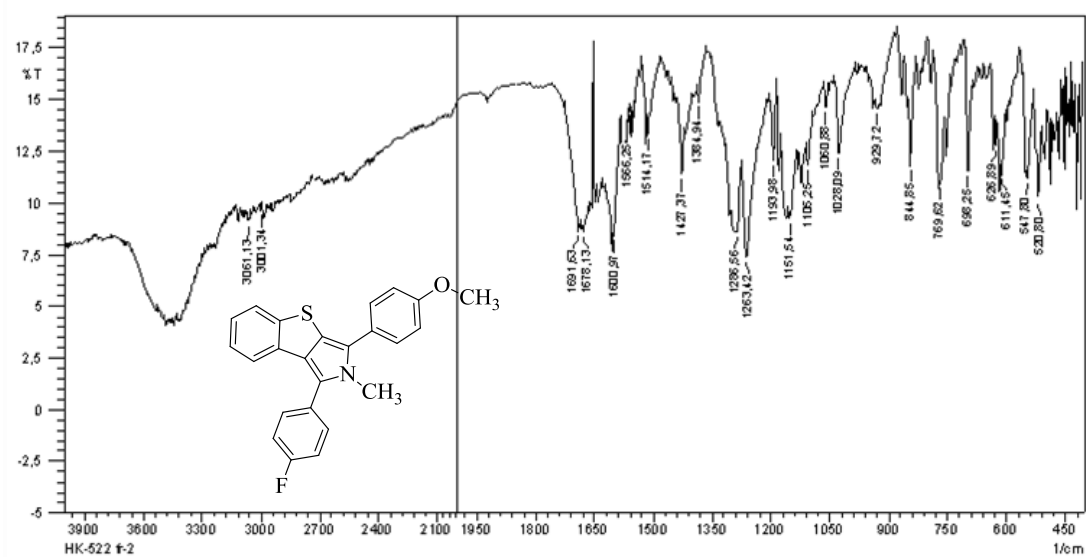
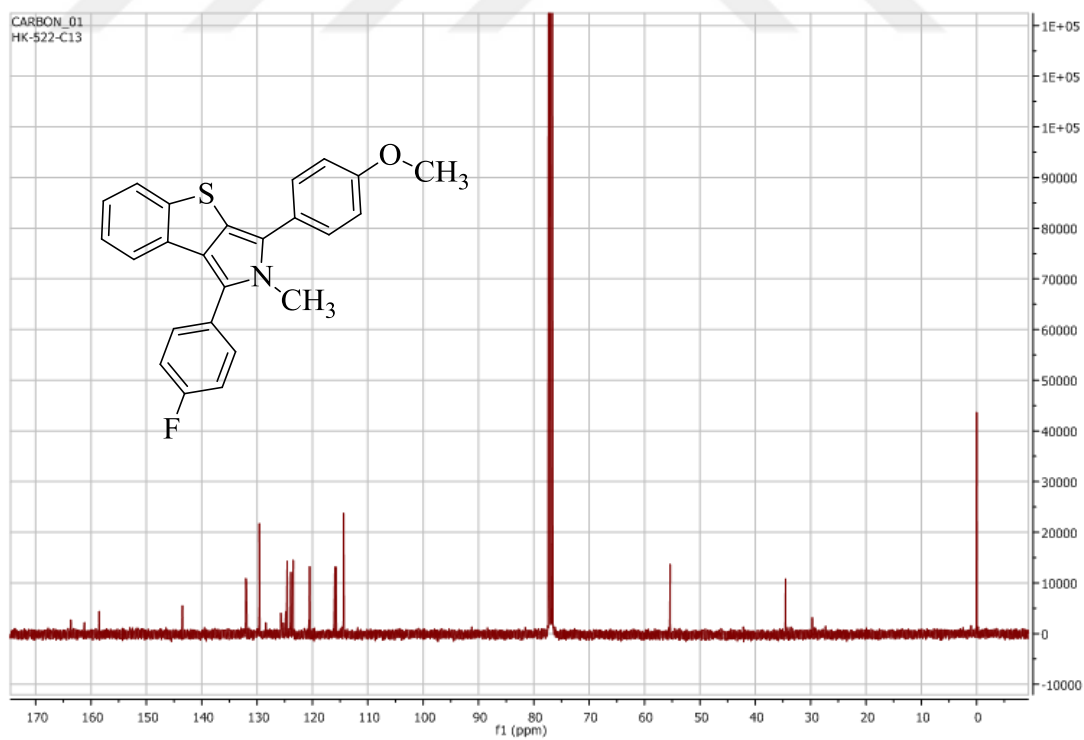
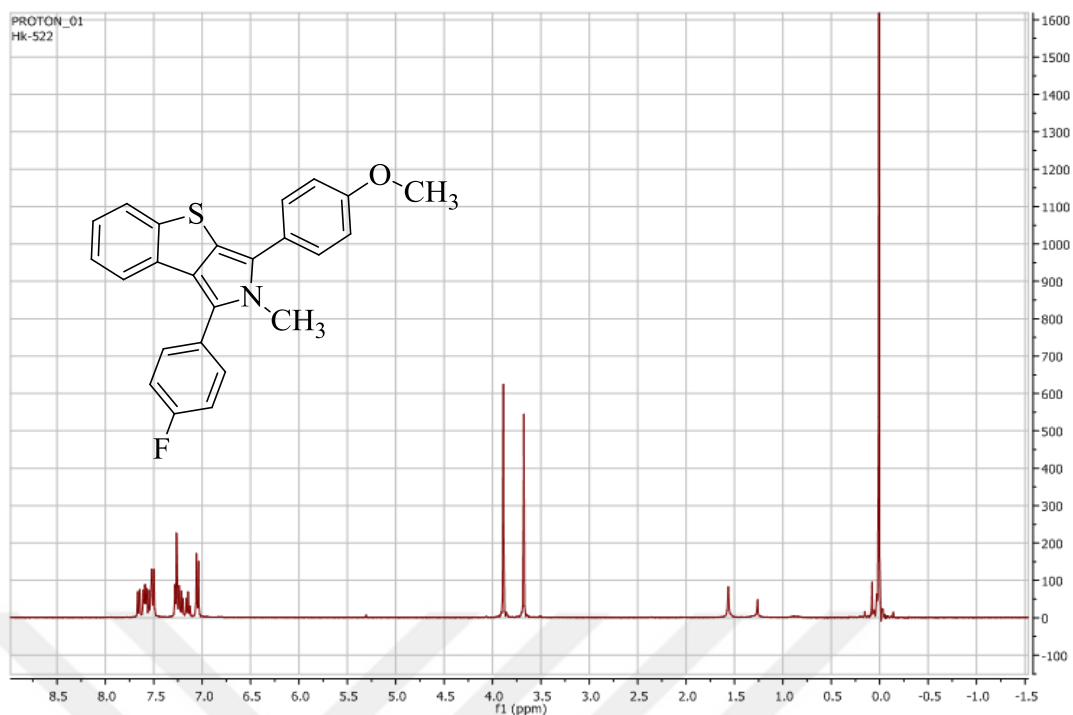


Figure A.46 IR Spectrum of compound 207c



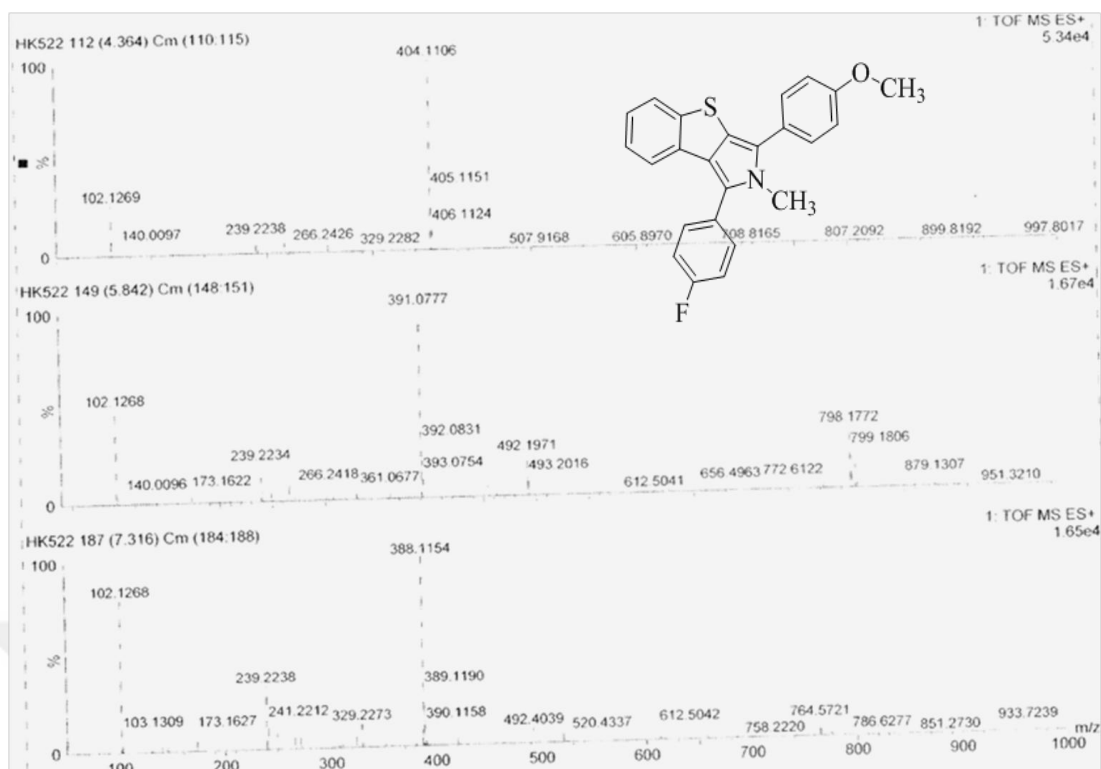


Figure A.49 MASS Spectrum of compound **207c**

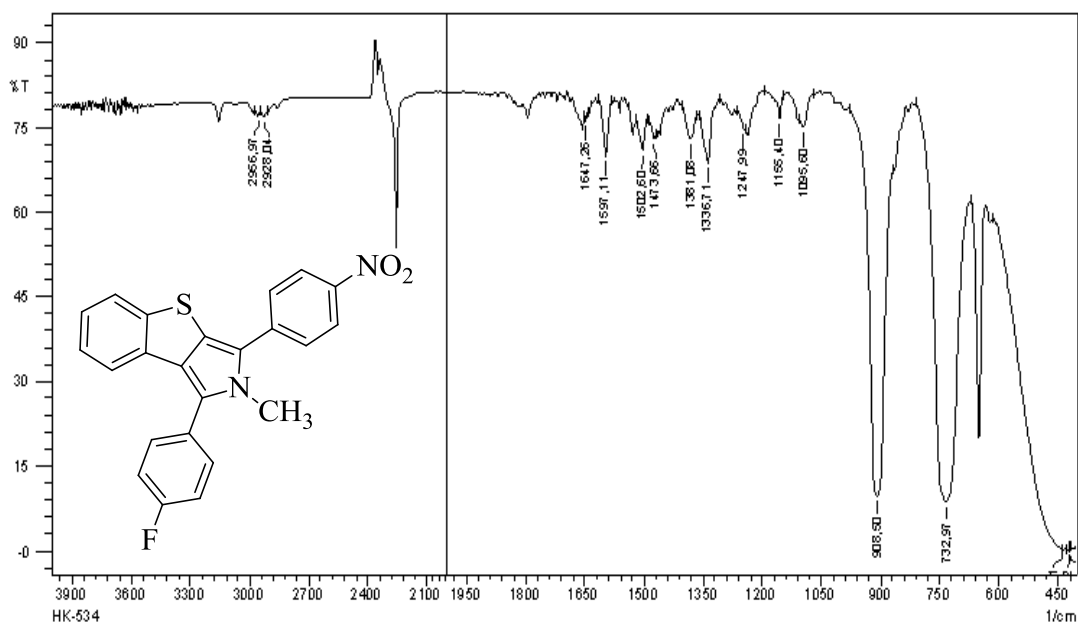


Figure A.50 IR Spectrum of compound **207d**

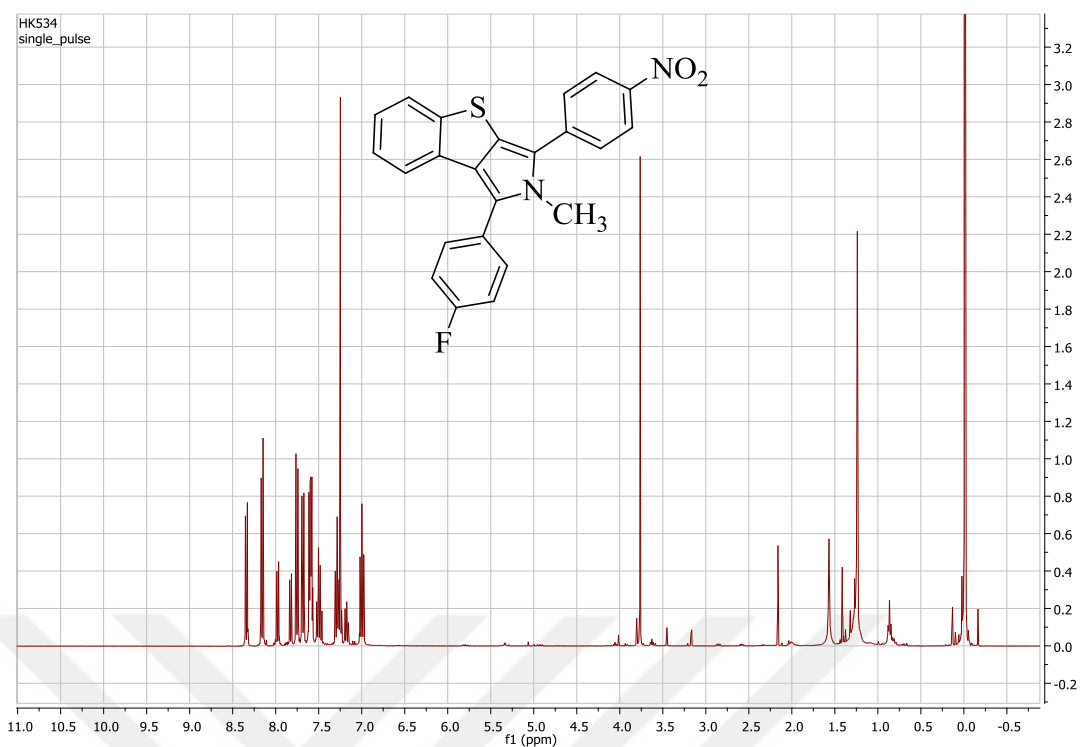


Figure A.51 ^1H NMR Spectrum of compound 207d

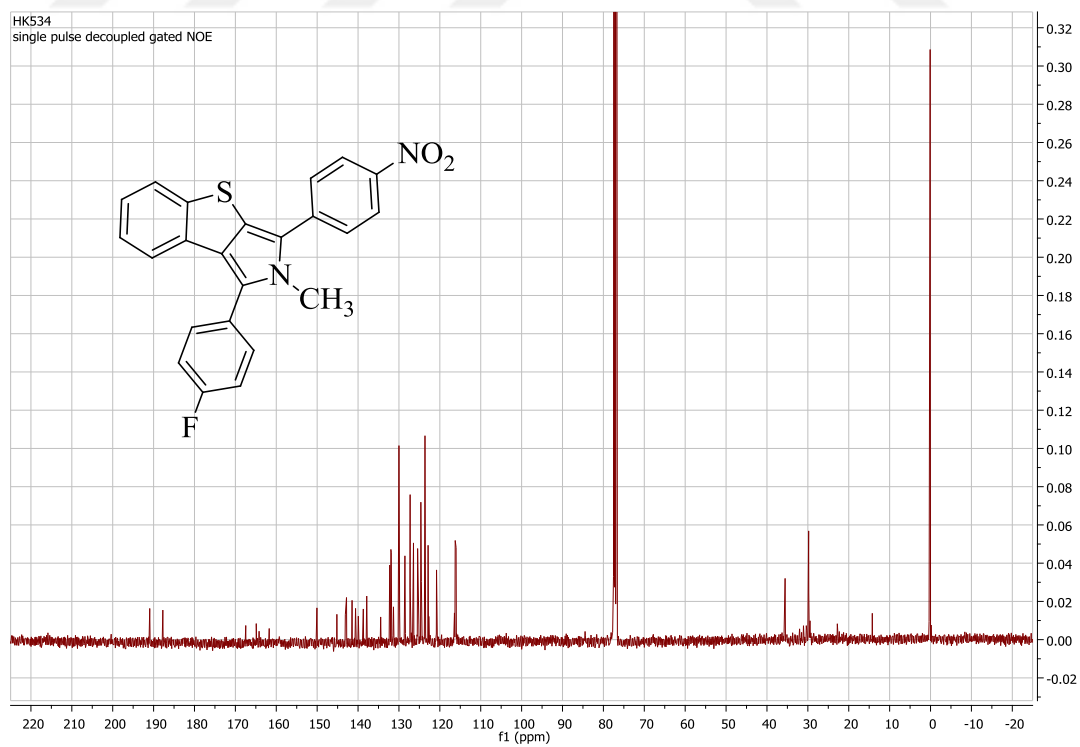


Figure A.52 ^{13}C NMR Spectrum of compound 207d

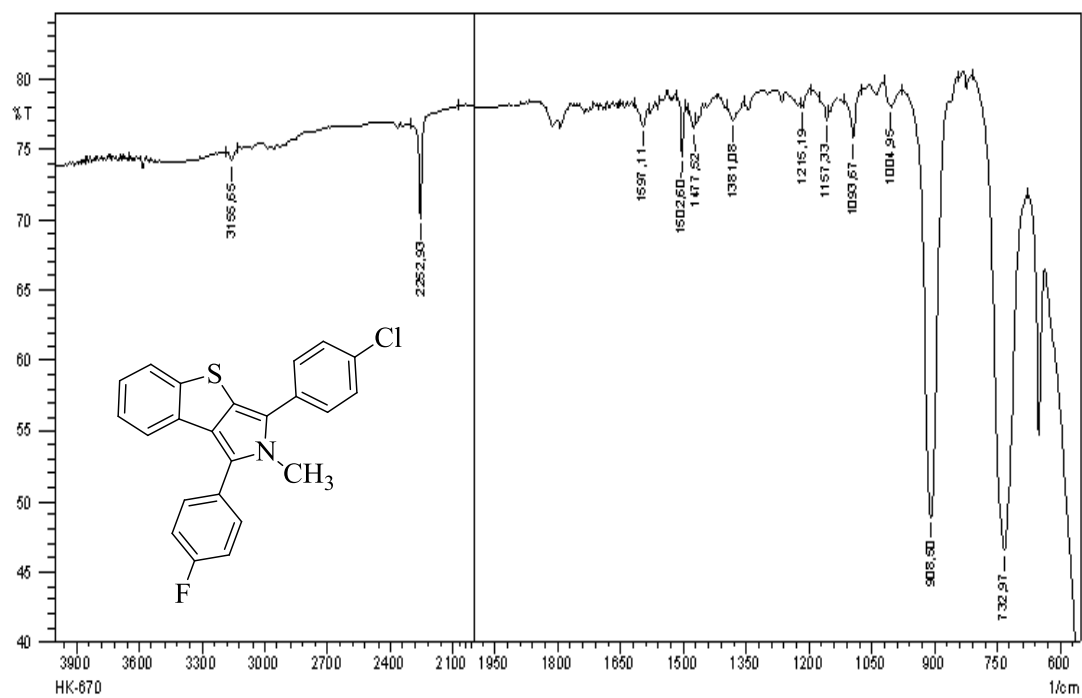


Figure A.53 IR Spectrum of compound **207e**

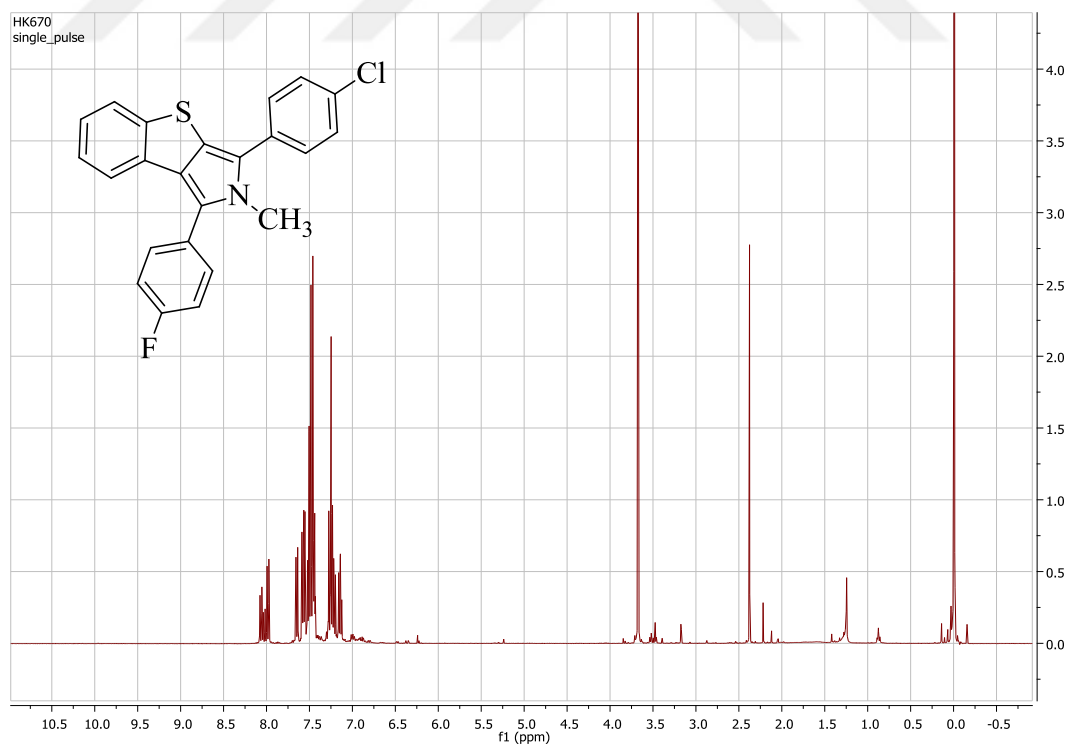


Figure A.54 ¹H NMR Spectrum of compound **207e**

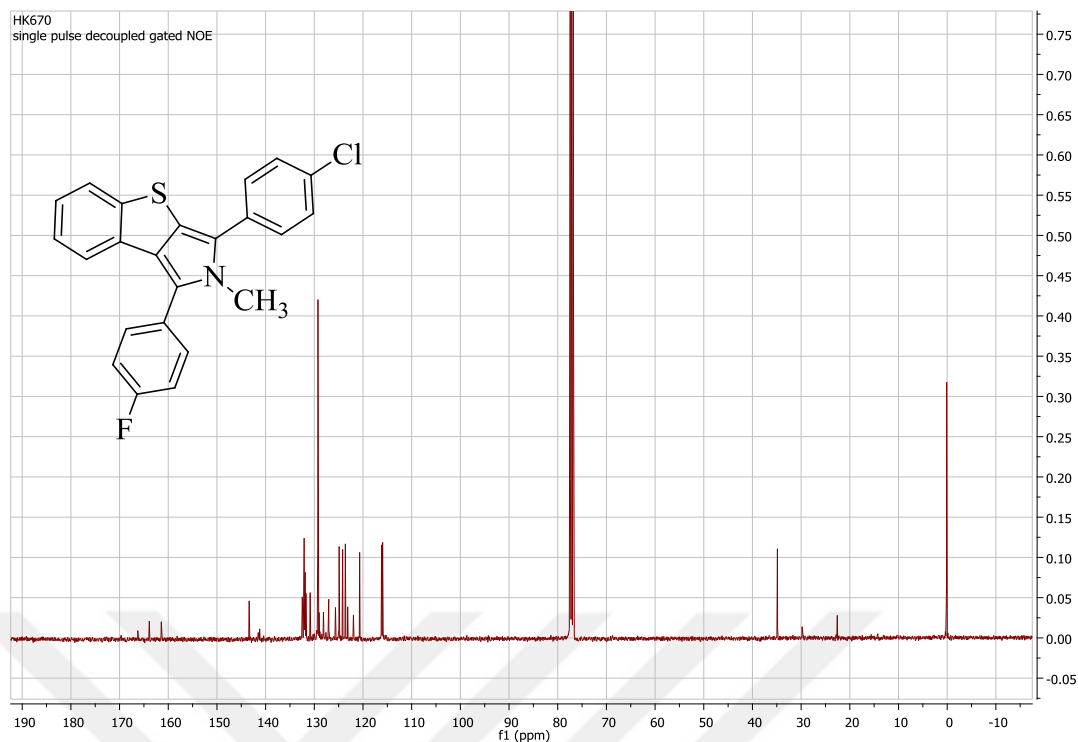


Figure A.55 ^{13}C NMR Spectrum of compound **207e**

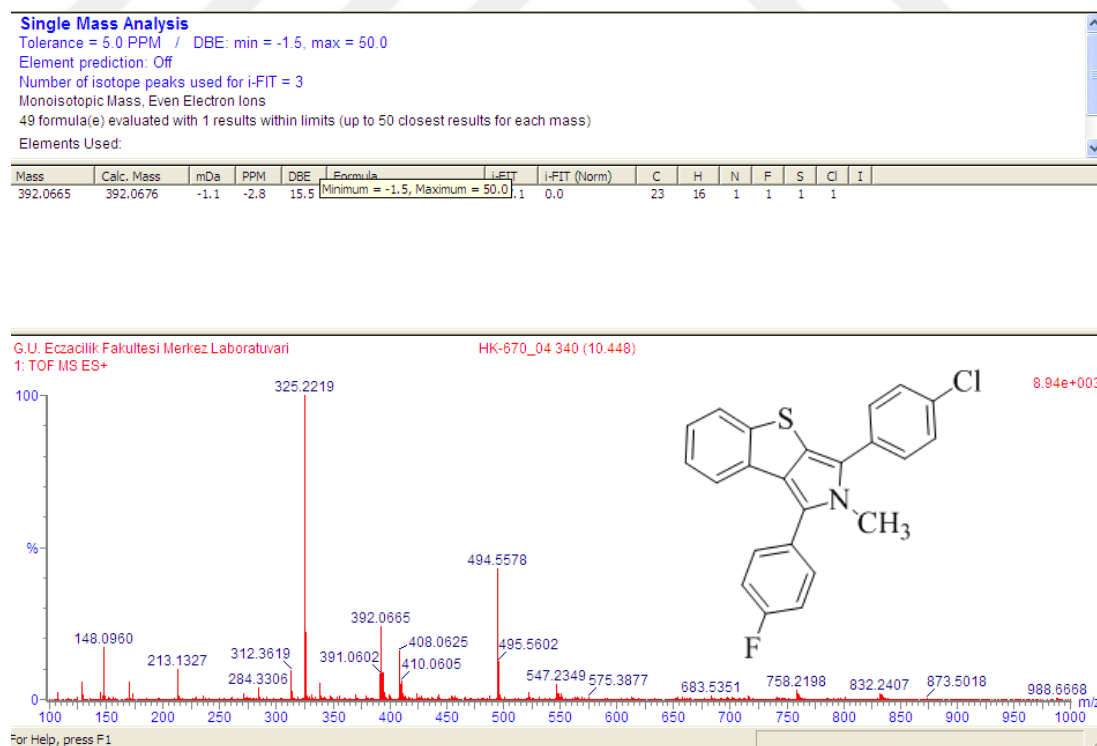


Figure A.56 MASS Spectrum of compound **207e**

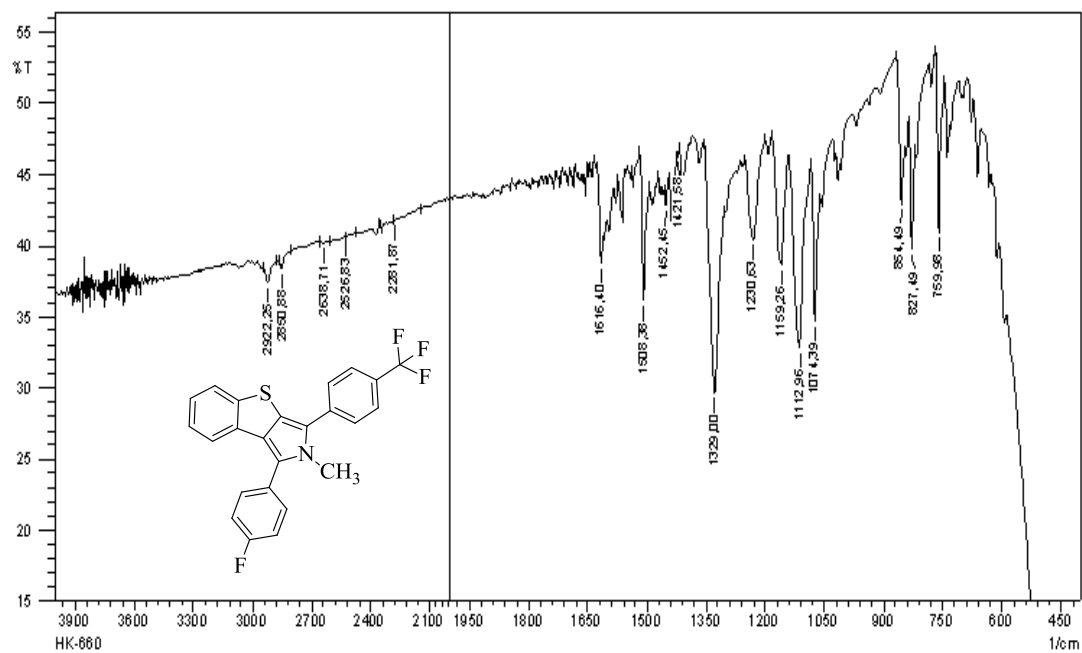


Figure A.57 IR Spectrum of compound **207f**

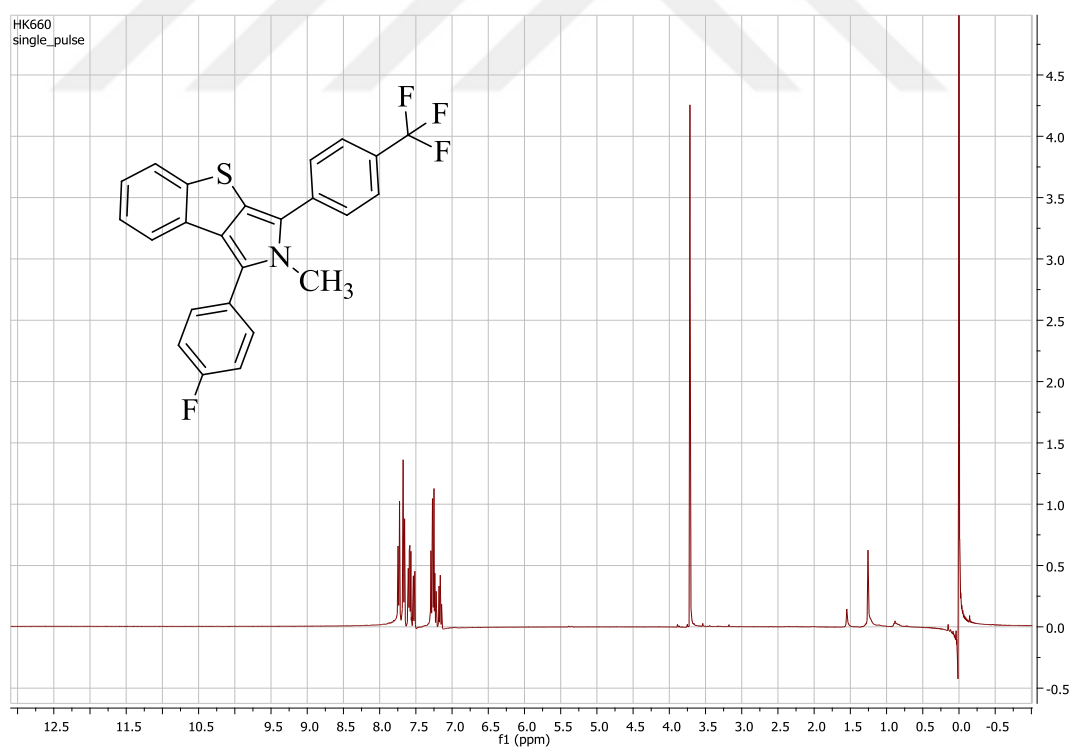


Figure A.58 ^1H NMR Spectrum of compound **207f**

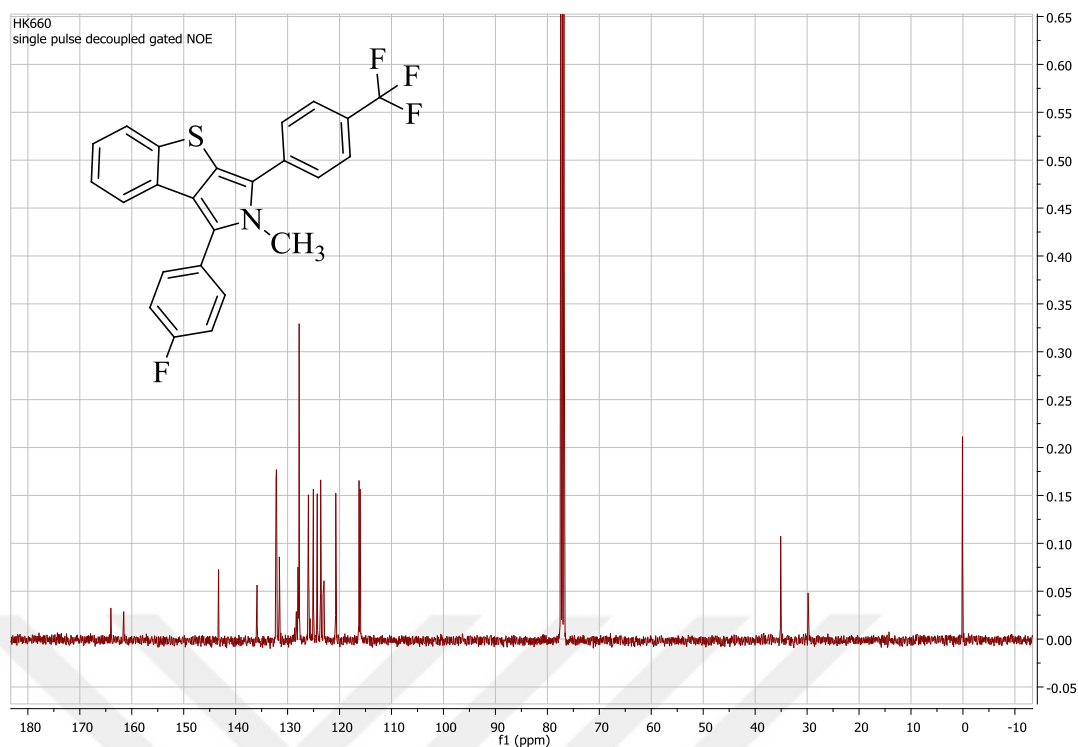


Figure A.59 ^{13}C NMR Spectrum of compound **207f**

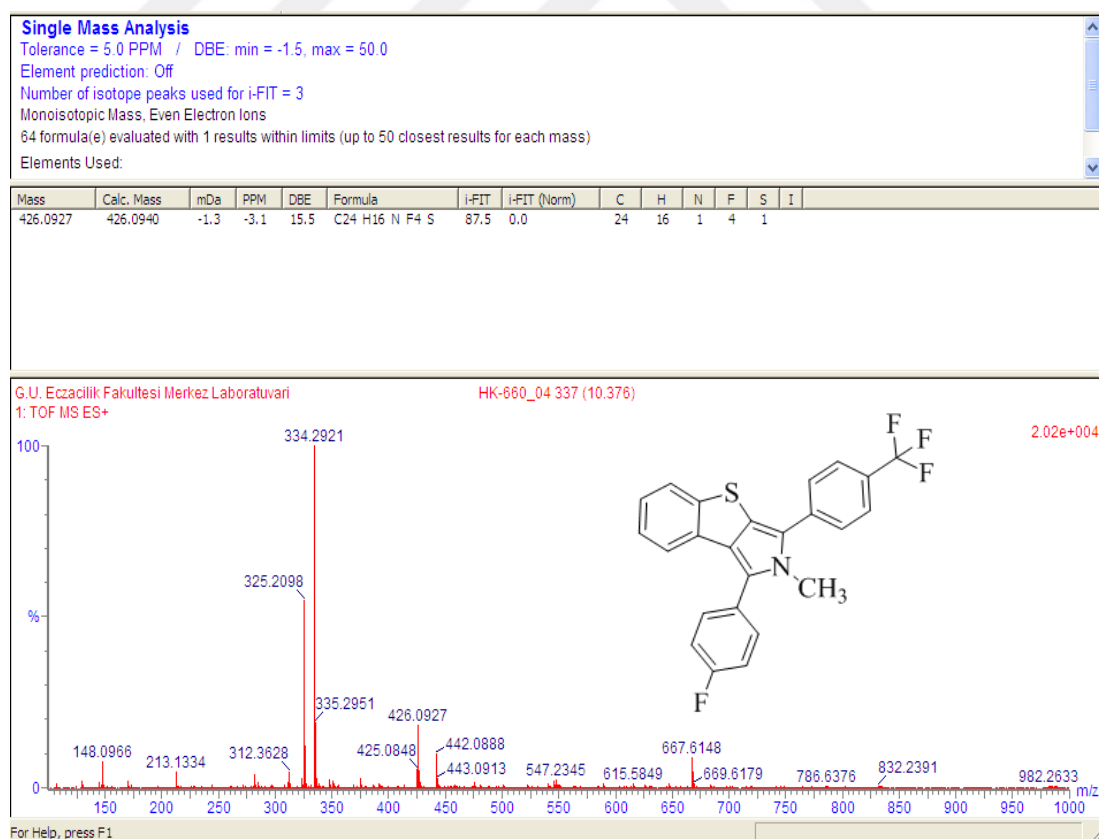


Figure A.60 MASS Spectrum of compound **207f**

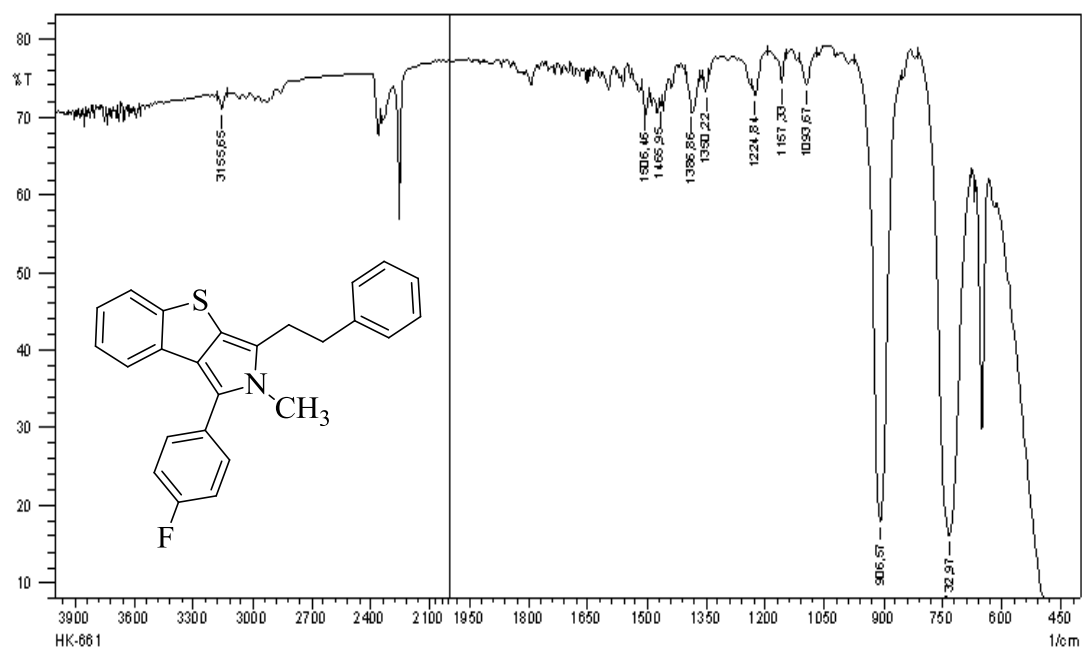


Figure A.61 IR Spectrum of compound **207g**

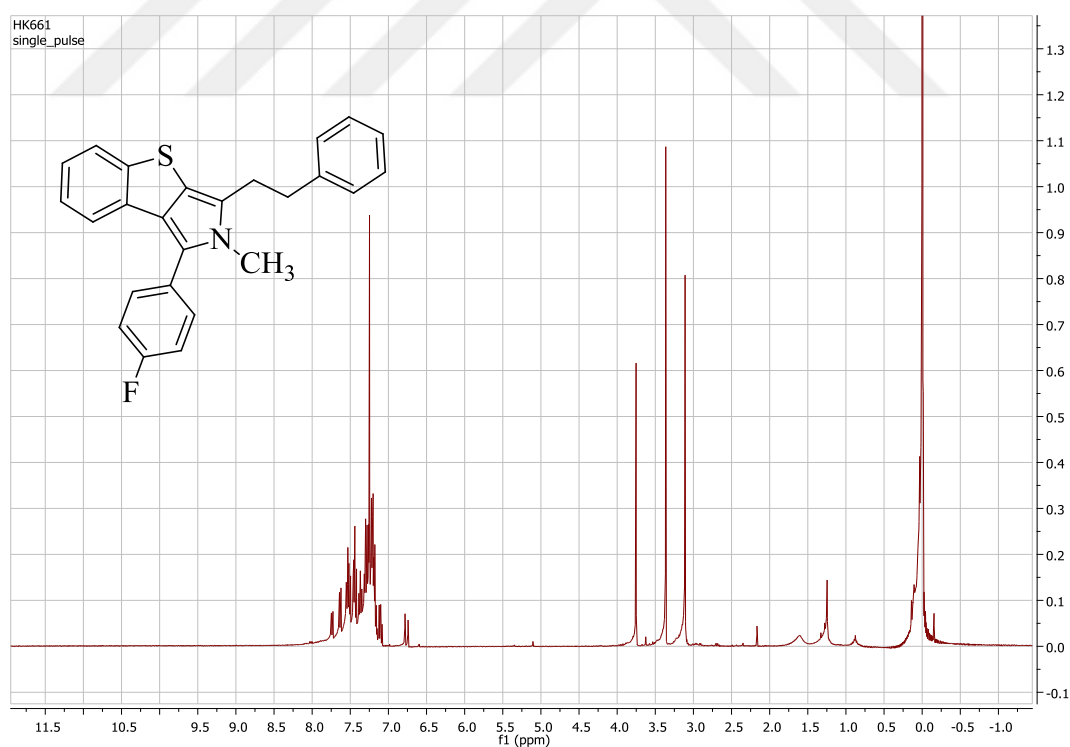


Figure A.62 ¹H NMR Spectrum of compound **207g**

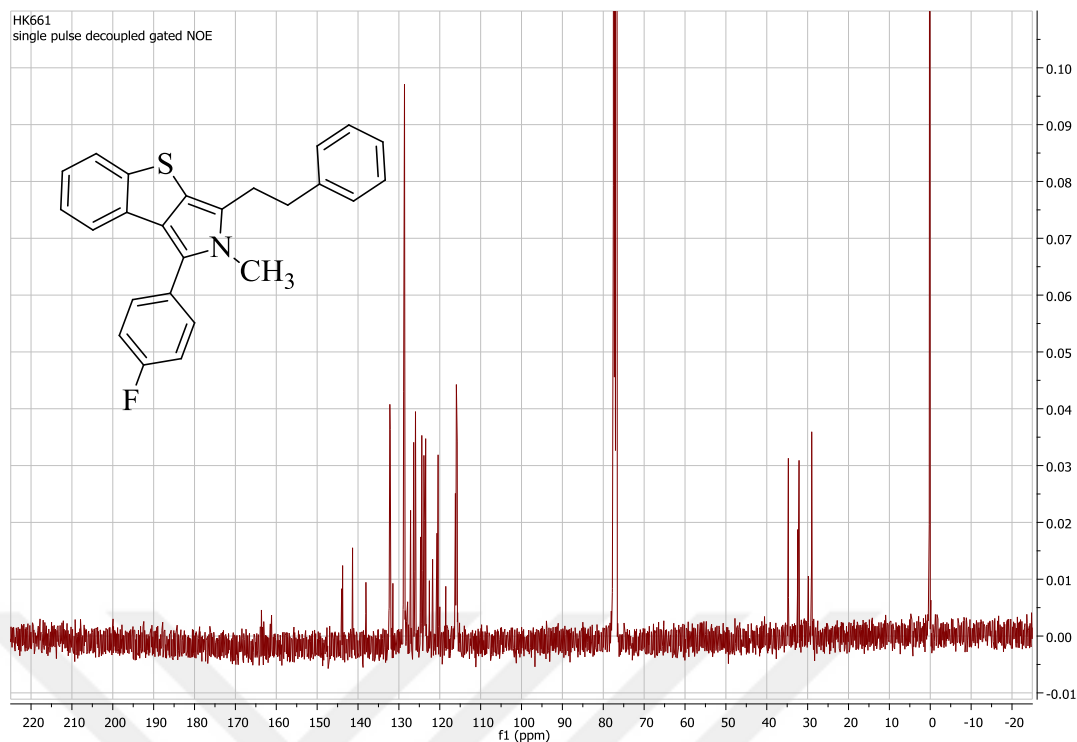


Figure A.63 ^{13}C NMR Spectrum of compound 207g

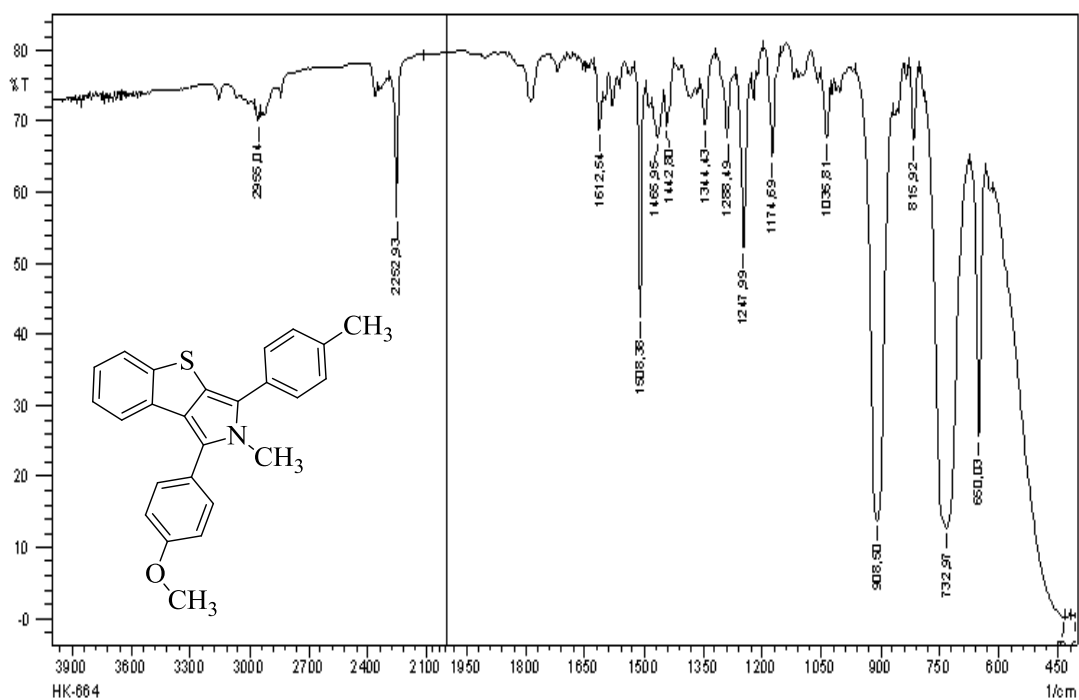


Figure A.64 IR Spectrum of compound 207h

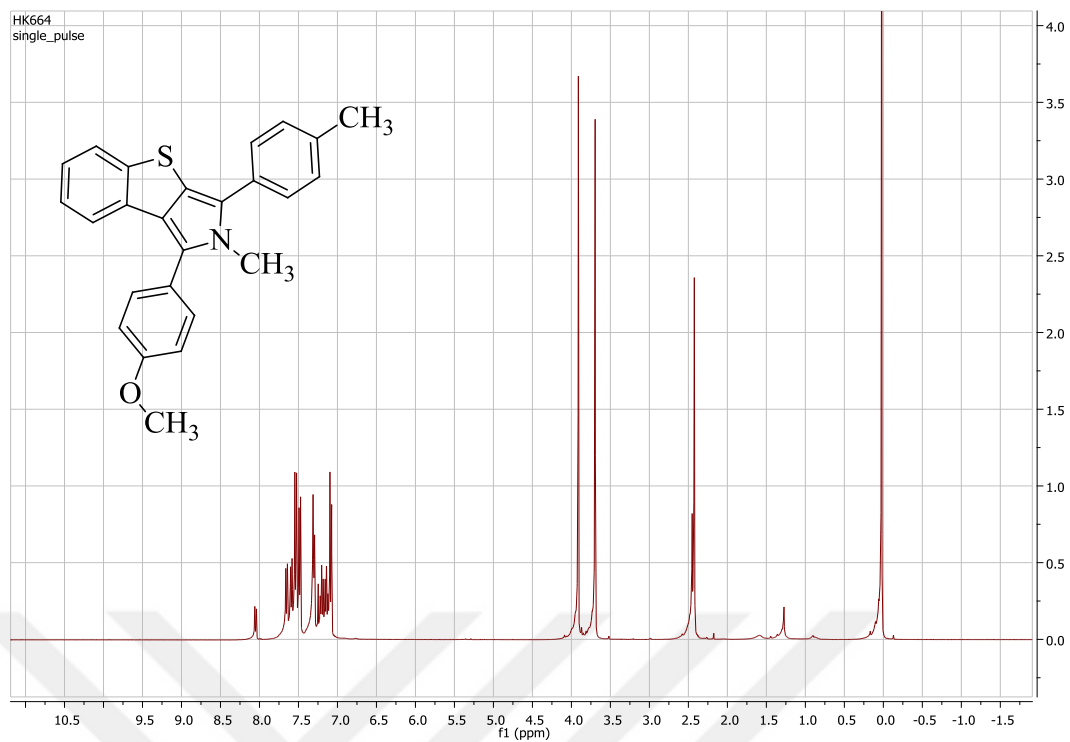


Figure A.65 ^1H NMR Spectrum of compound 207h

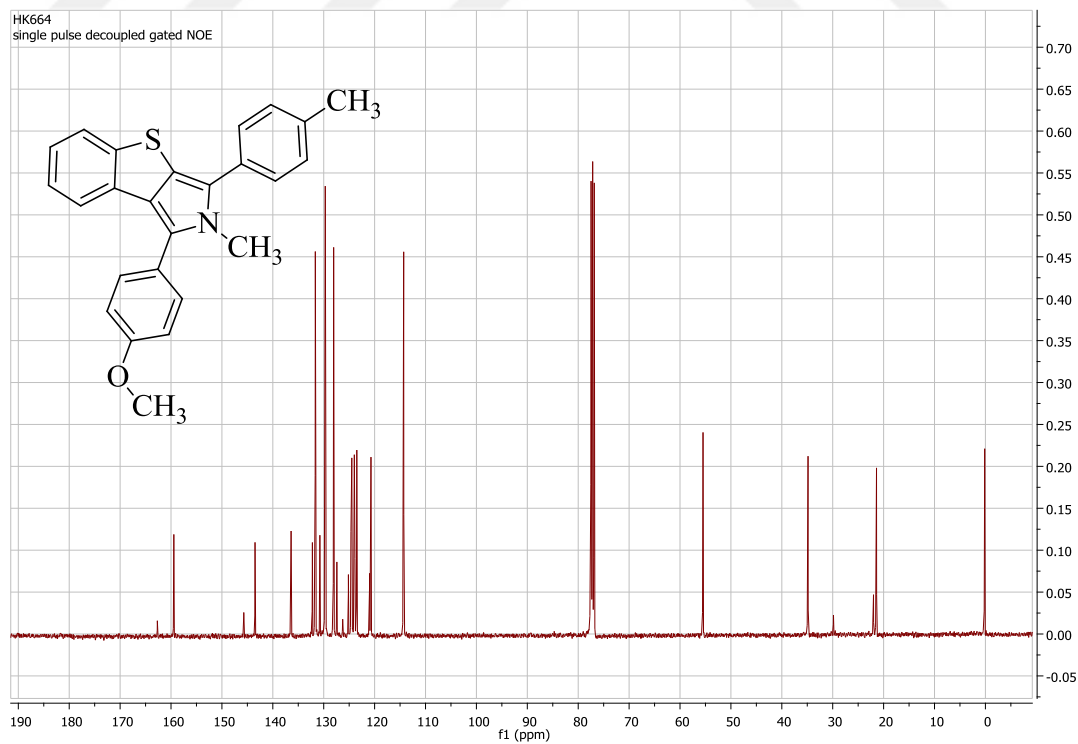


Figure A.66 ^{13}C NMR Spectrum of compound 207h

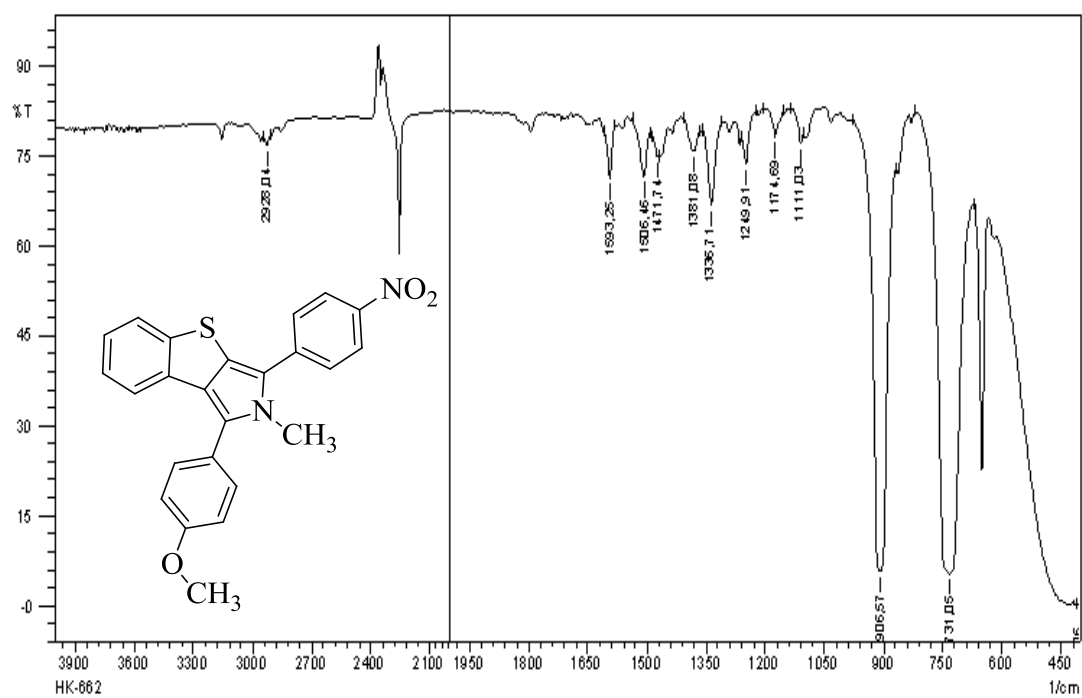


Figure A.67 IR Spectrum of compound **207i**

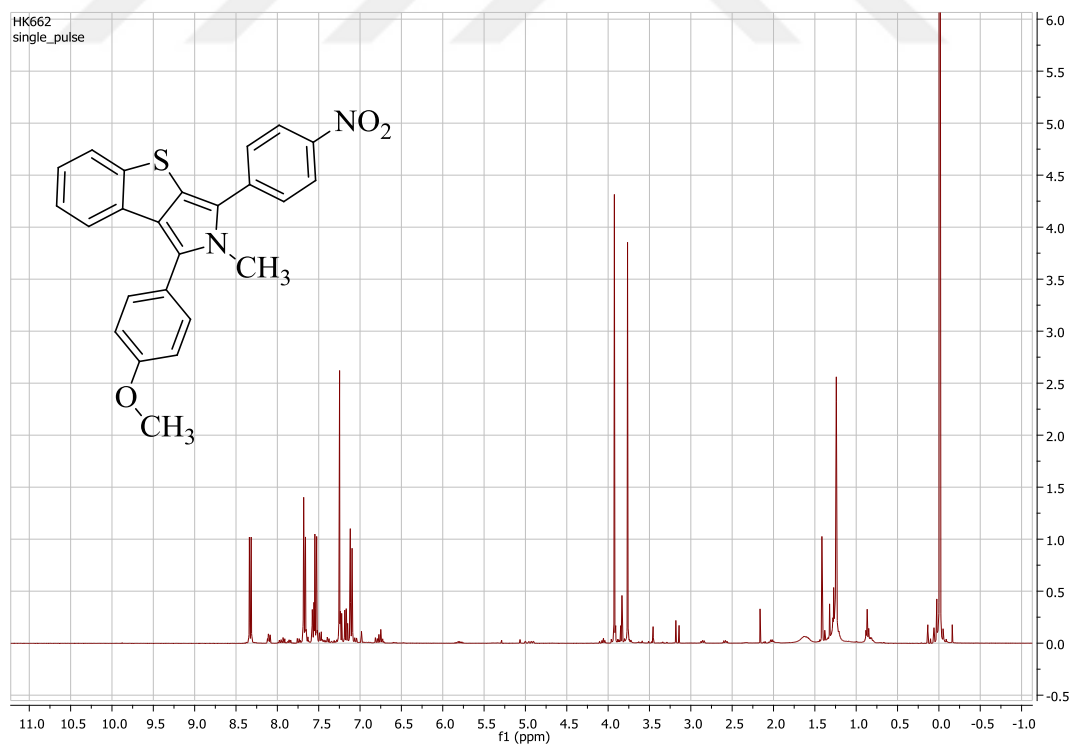


Figure A.68 ^1H NMR Spectrum of compound **207i**

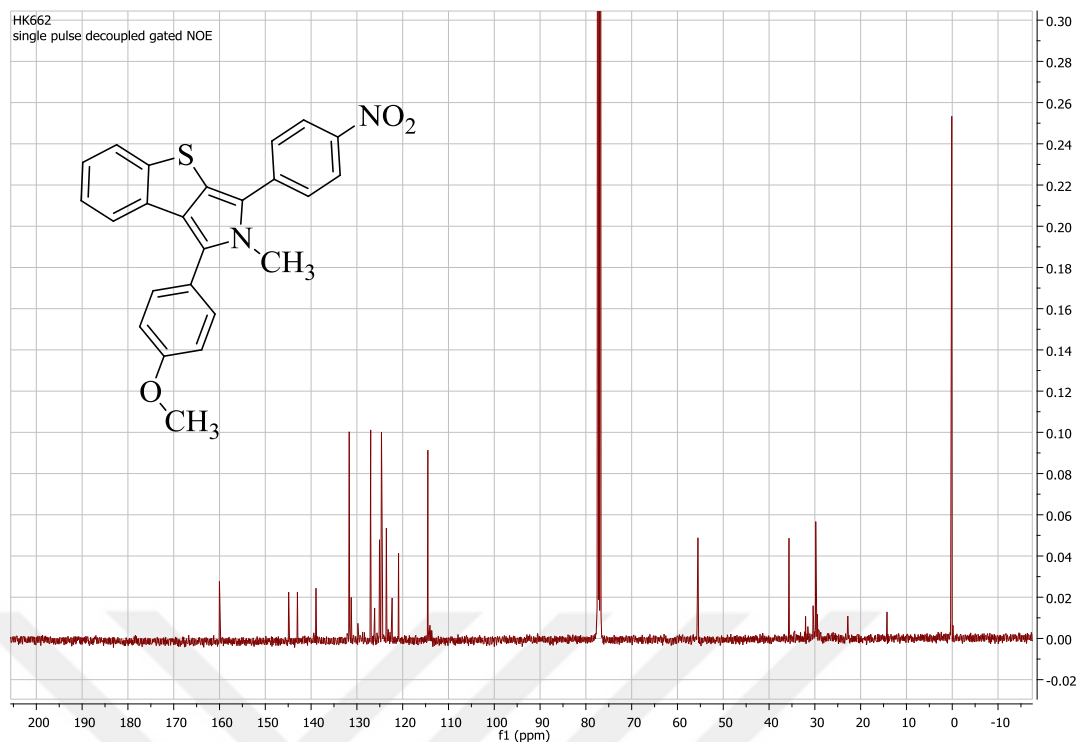


Figure A.69 ^{13}C NMR Spectrum of compound 207i

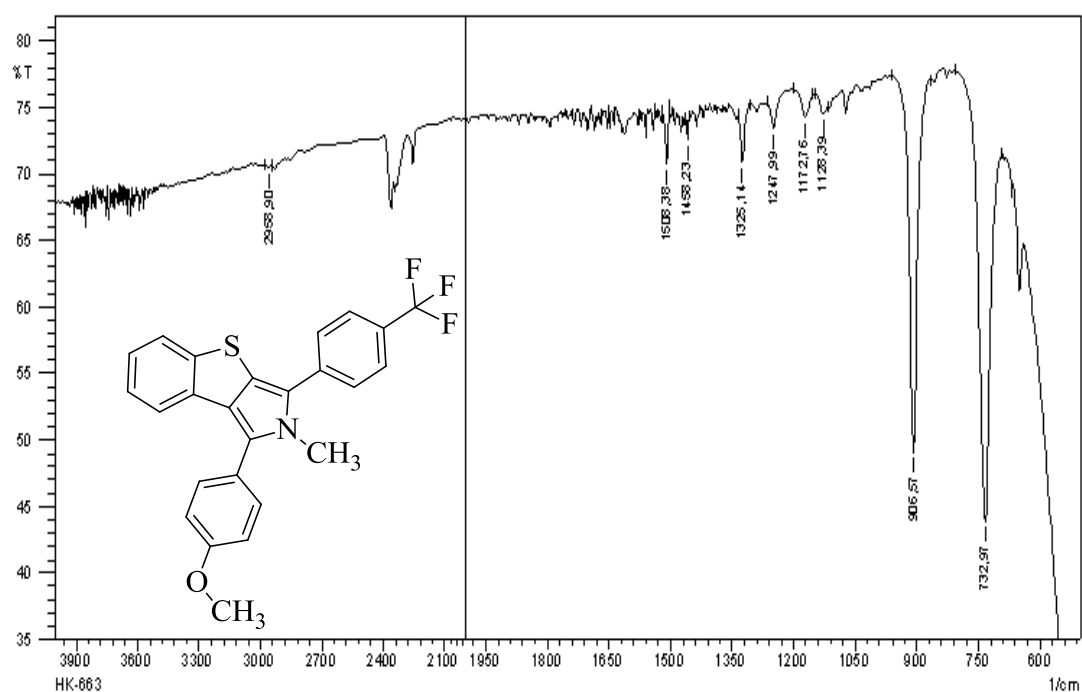


Figure A.70 IR Spectrum of compound 207j

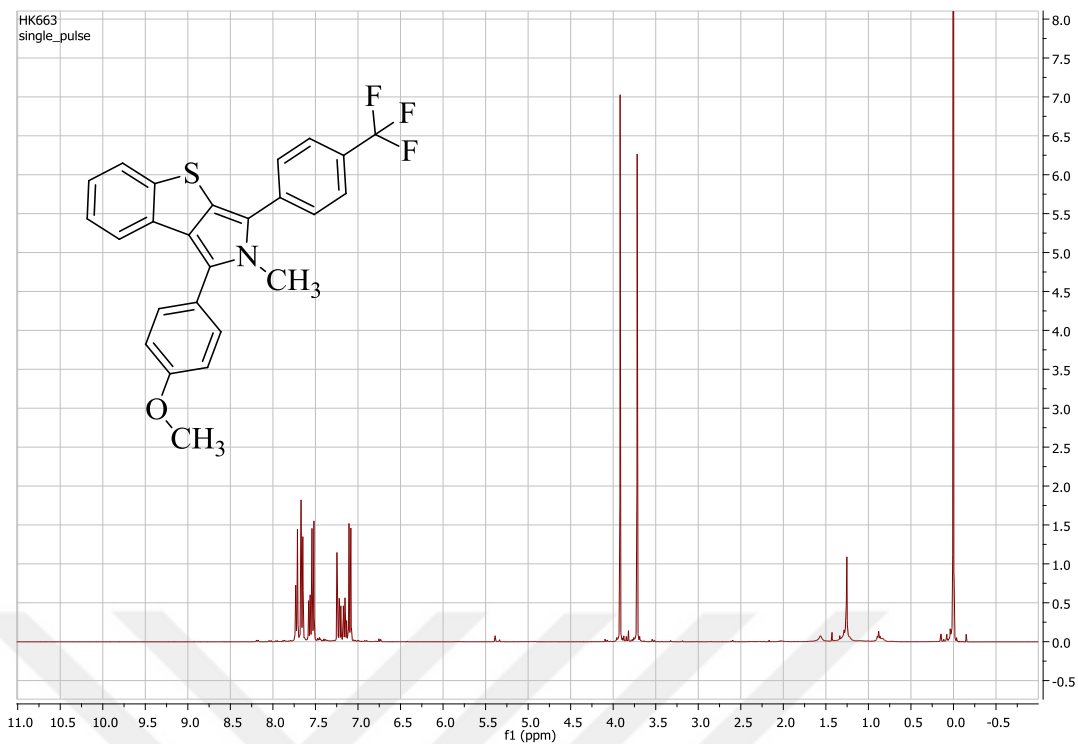


Figure A.71 ¹H NMR Spectrum of compound **207j**

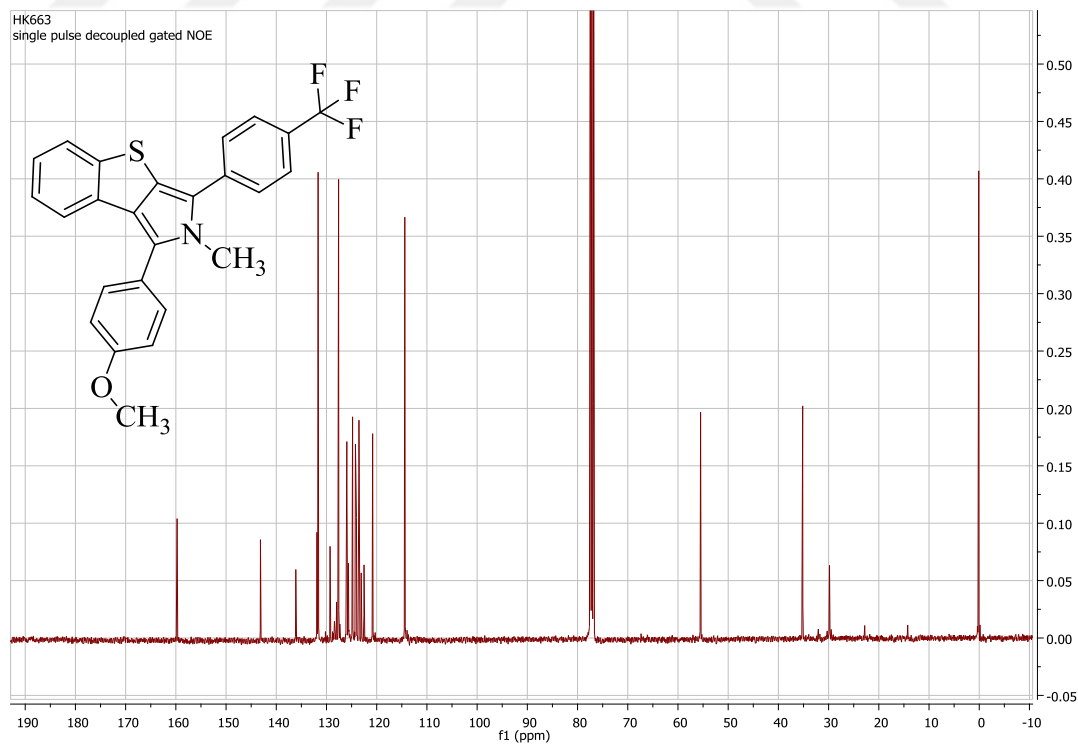


Figure A.72 ¹³C NMR Spectrum of compound **207j**

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

111 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

Mass	Calc. Mass	mDa	PPM	DBE	Formula	i-FIT	i-FIT (Norm)	C	H	N	O	S	I	F
438.1120	438.1139	-1.9	-4.3	15.5	C ₂₅ H ₁₉ N O S F ₃	71.2	0.0	25	19	1	1	1		3

G.U. Eczacılık Fakültesi Merkez Laboratuvarı

HK-663 338 (10.397)

1: TOF MS ES+

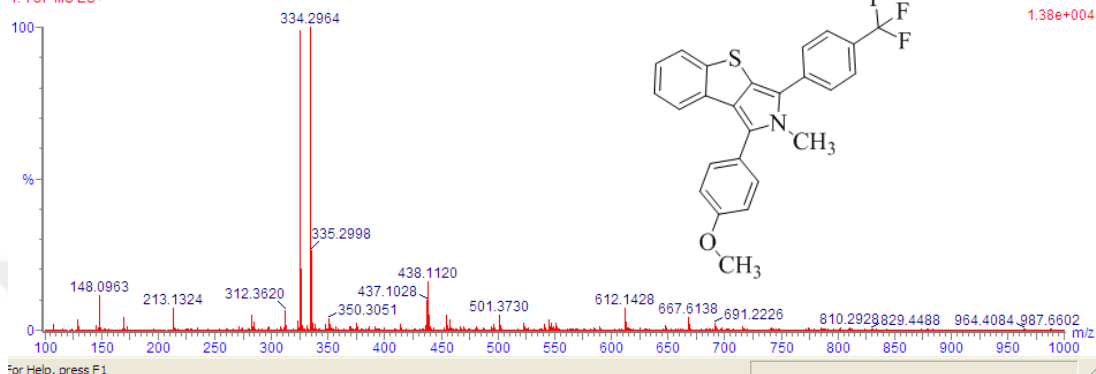


Figure A.73 MASS Spectrum of compound 207j

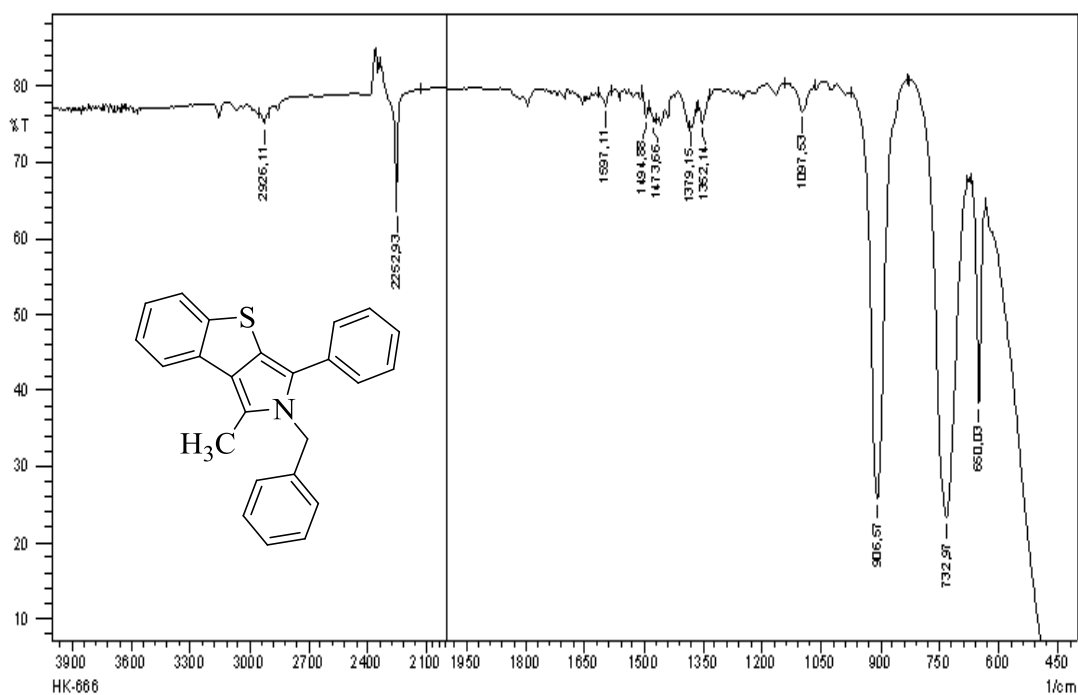


Figure A.74 IR Spectrum of compound 207k

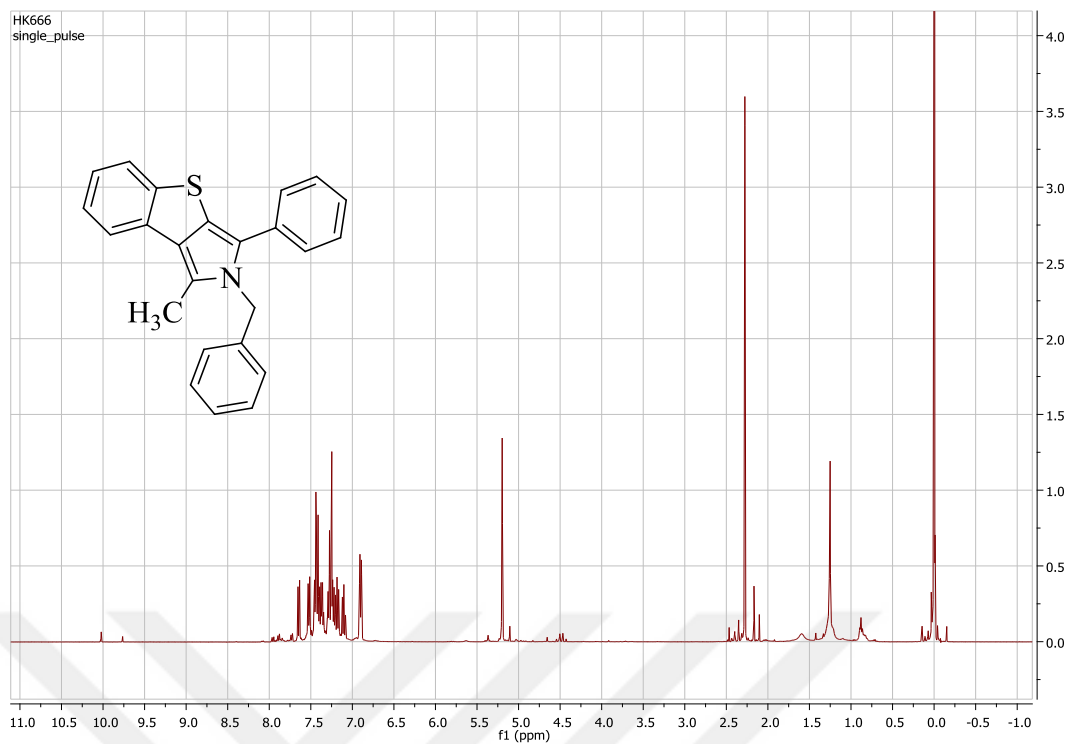


Figure A.75 ^1H NMR Spectrum of compound **207k**

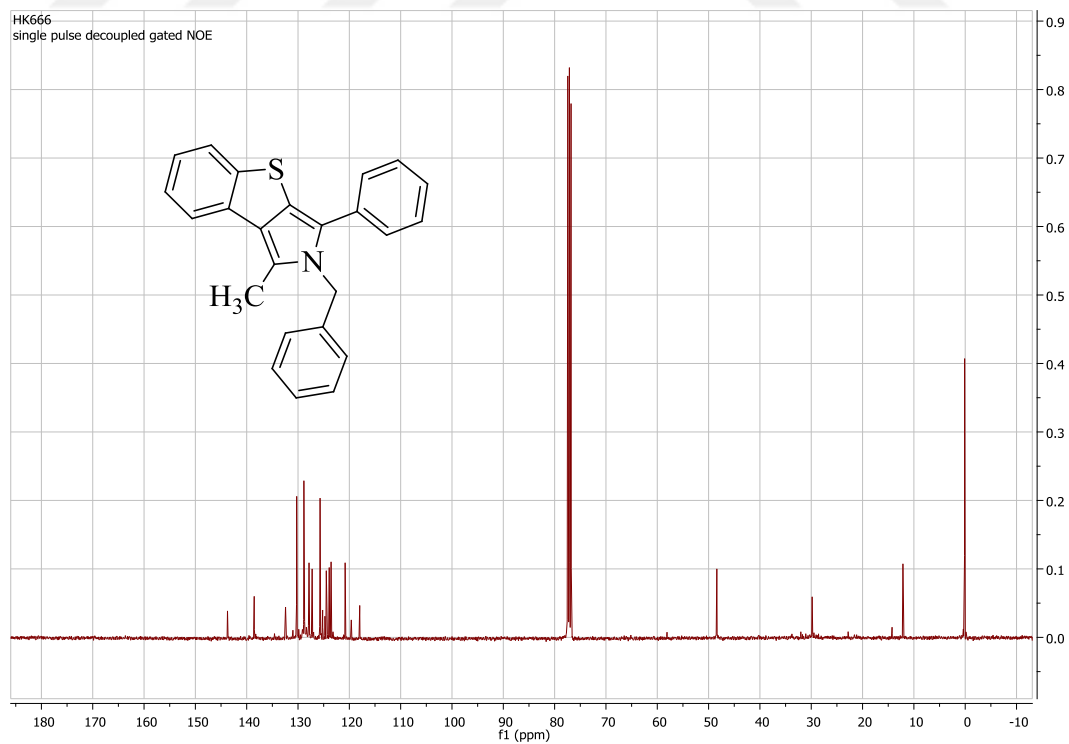


Figure A.76 ^{13}C NMR Spectrum of compound **207k**

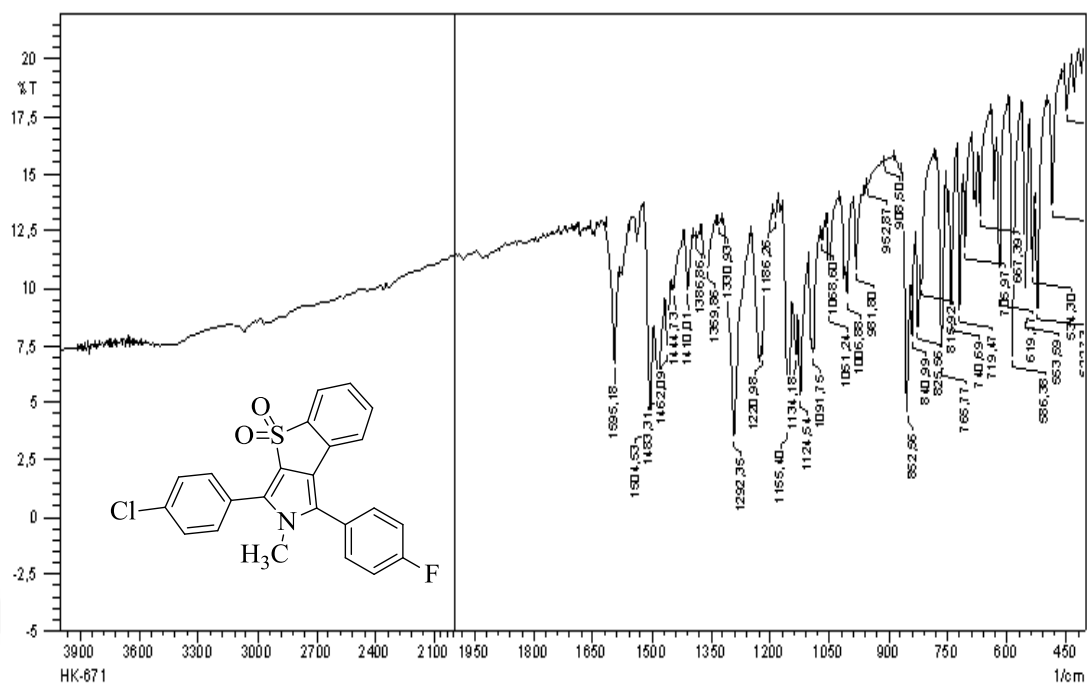


Figure A.77 IR Spectrum of compound **208e**

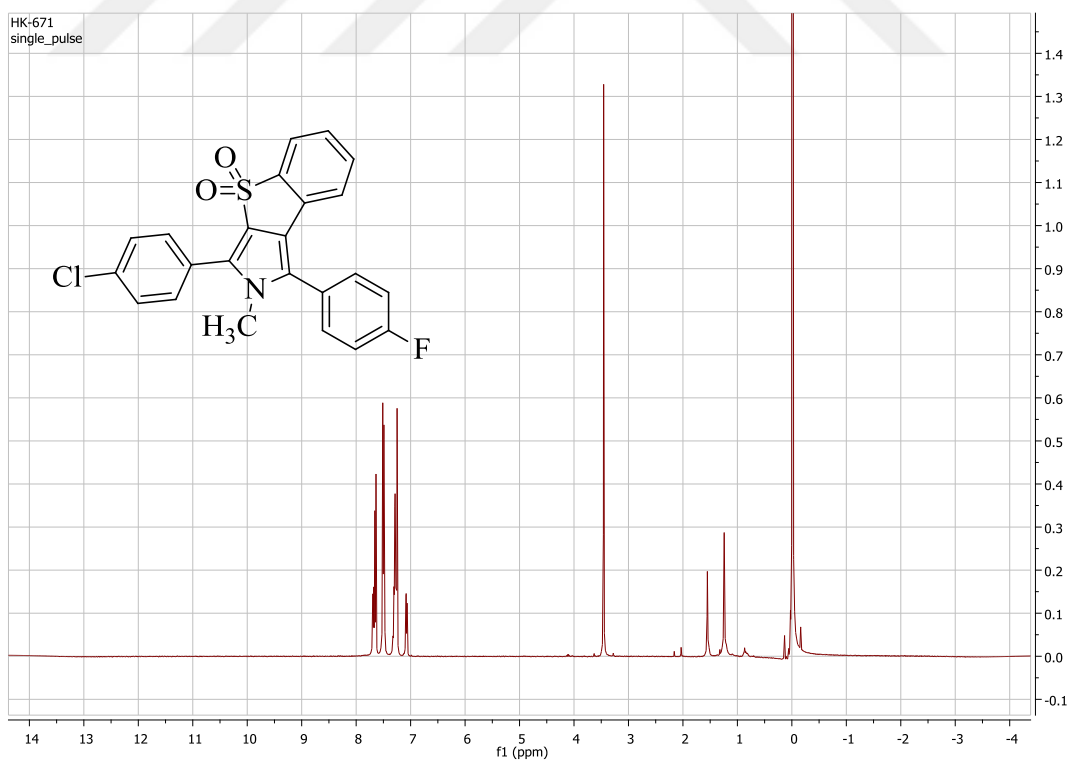


Figure A.78 ^1H NMR Spectrum of compound **208e**

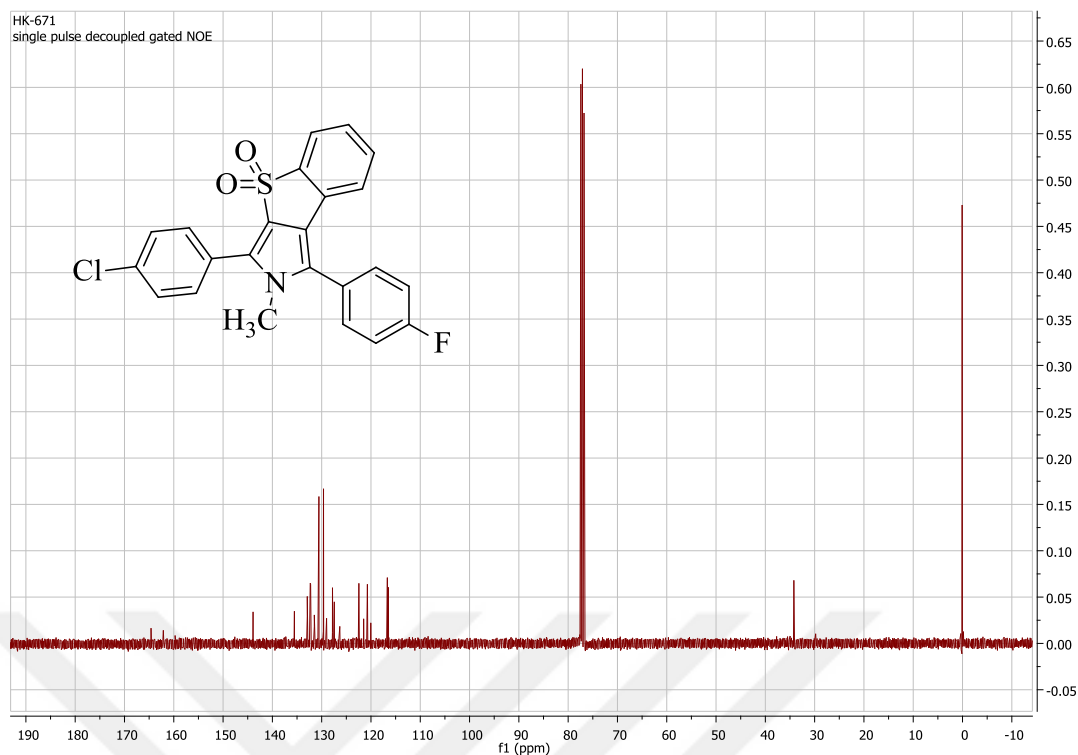


Figure A.79 ^{13}C NMR Spectrum of compound **208e**

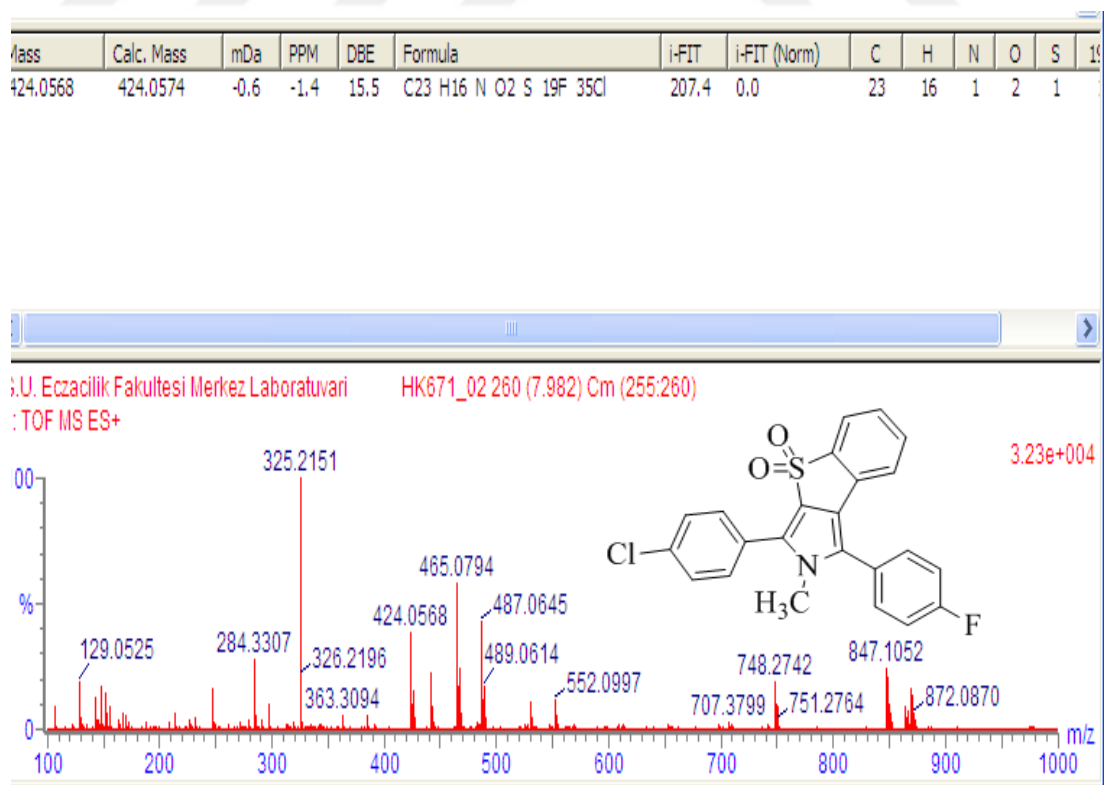


Figure A.80 MASS Spectrum of compound **208e**

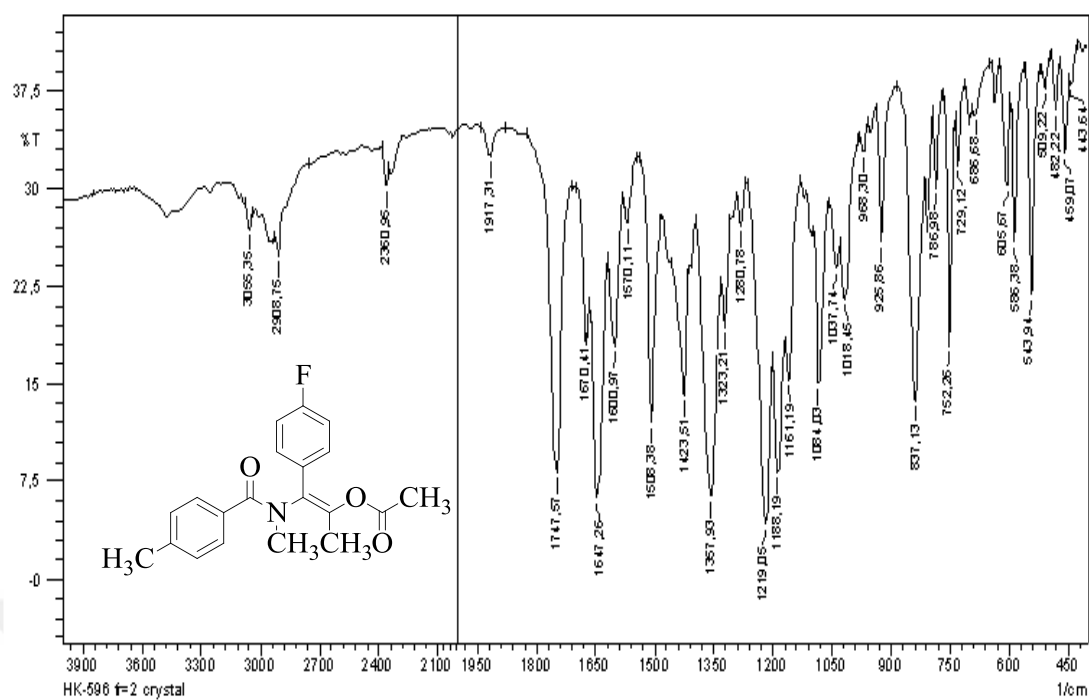


Figure A.81 IR Spectrum of compound **209**

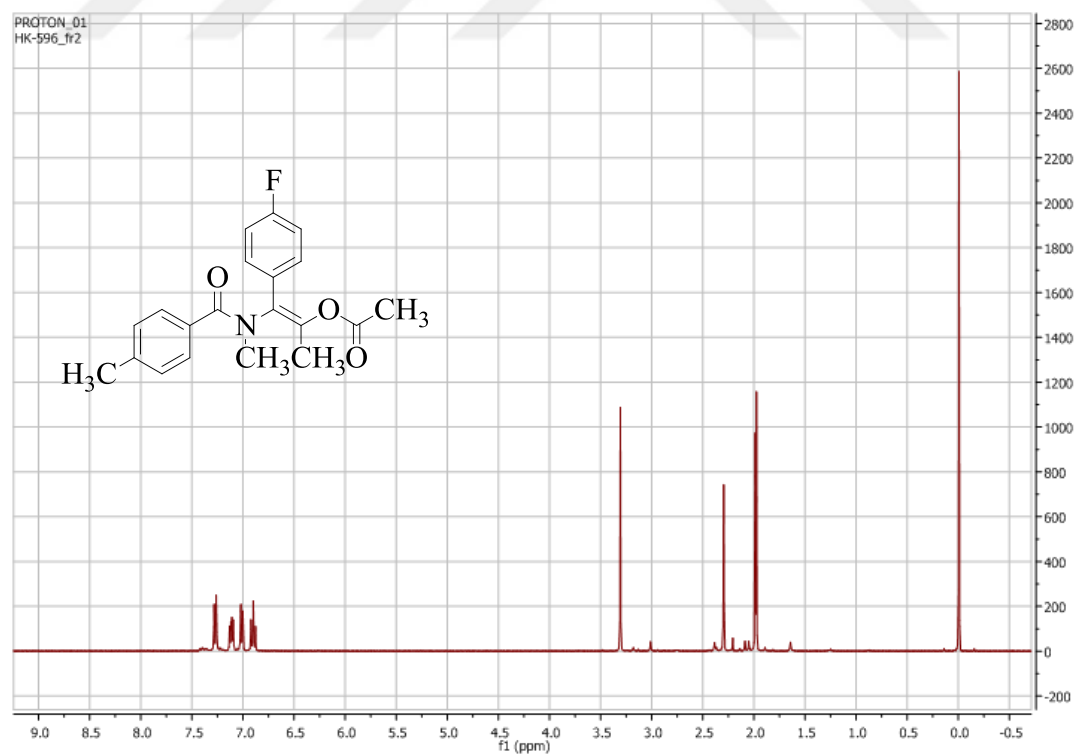


Figure A.82 ^1H NMR Spectrum of compound **209**

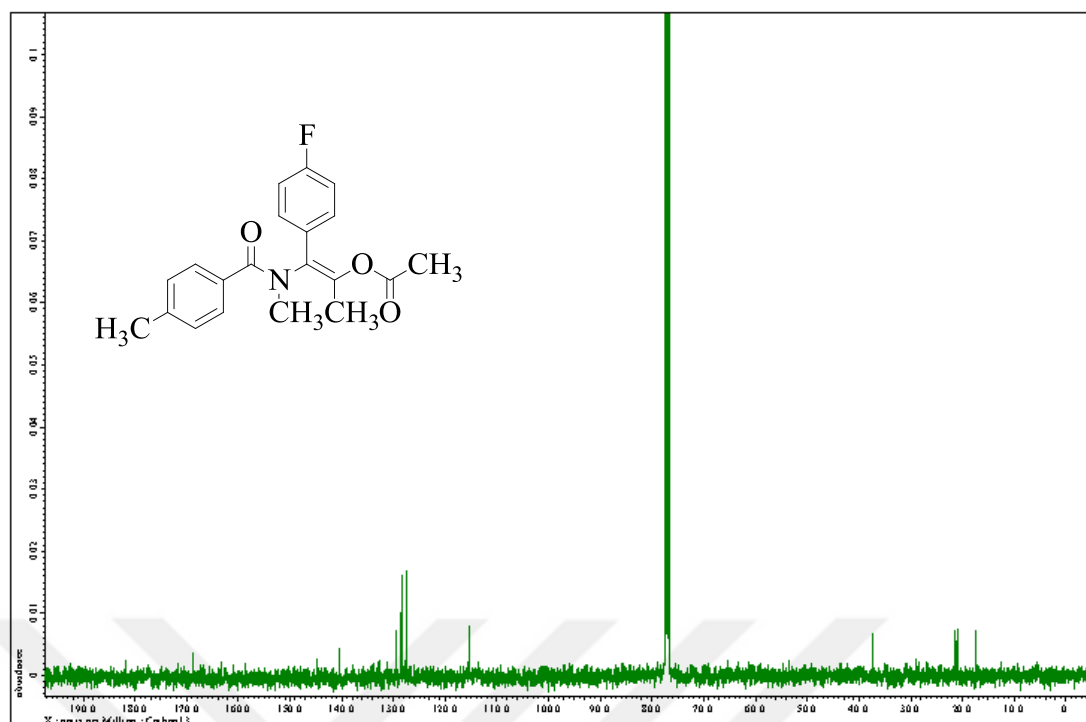


Figure A.83 ^{13}C NMR Spectrum of compound 209

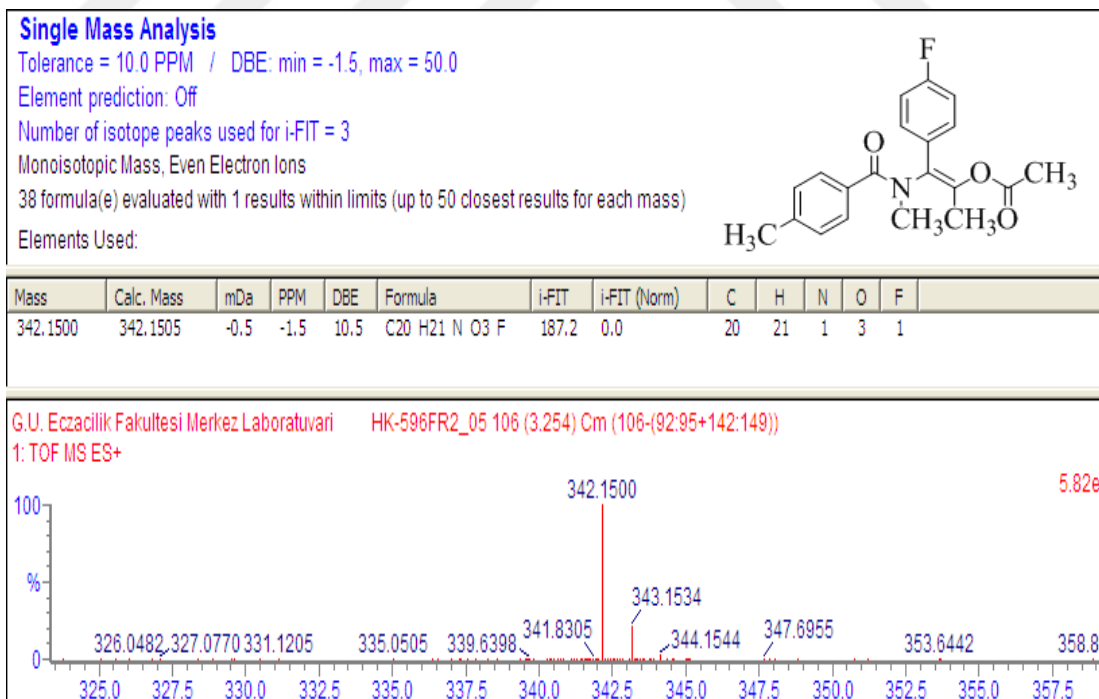


Figure A.84 MASS Spectrum of compound 209

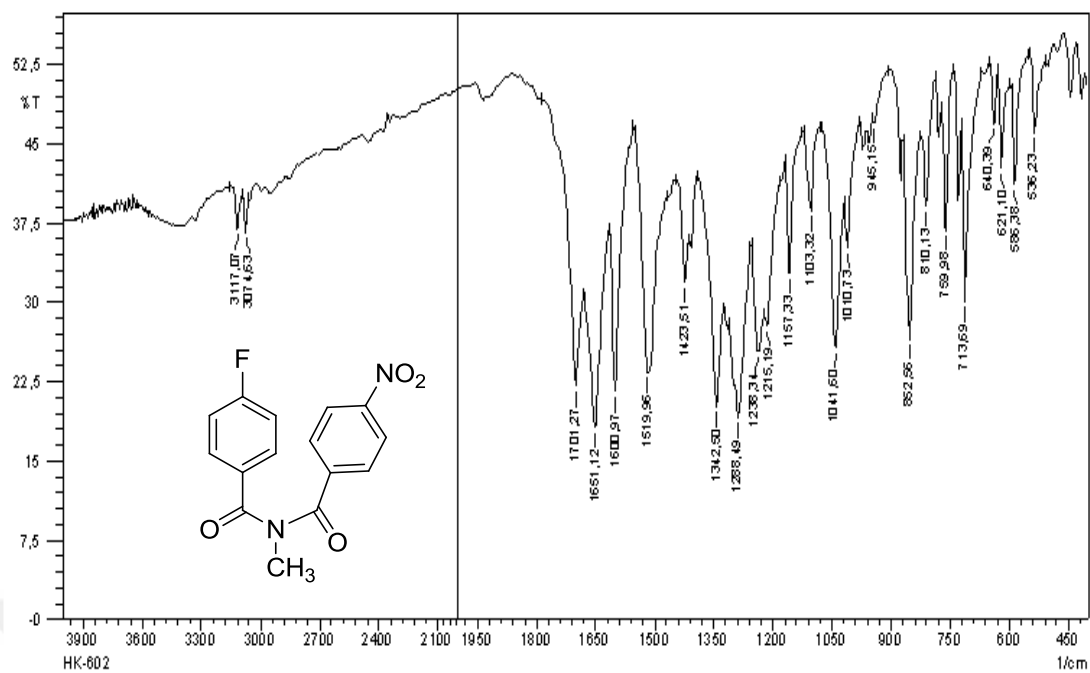


Figure A.85 IR Spectrum of compound **210d**

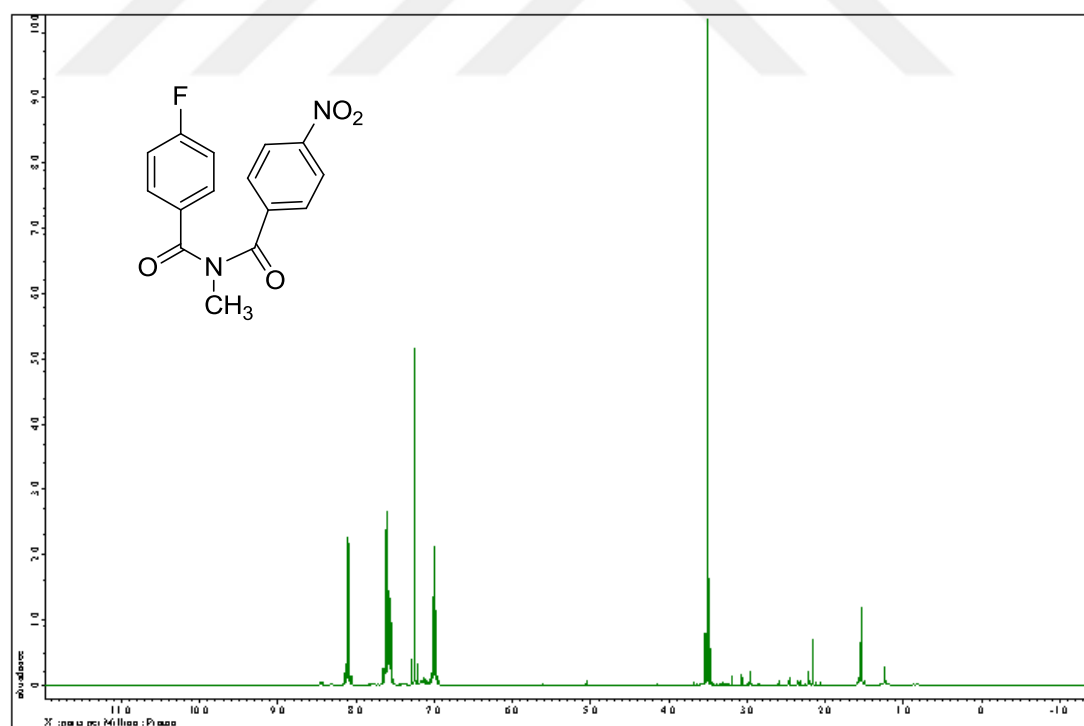


Figure A.86 ¹H NMR Spectrum of compound **210d**

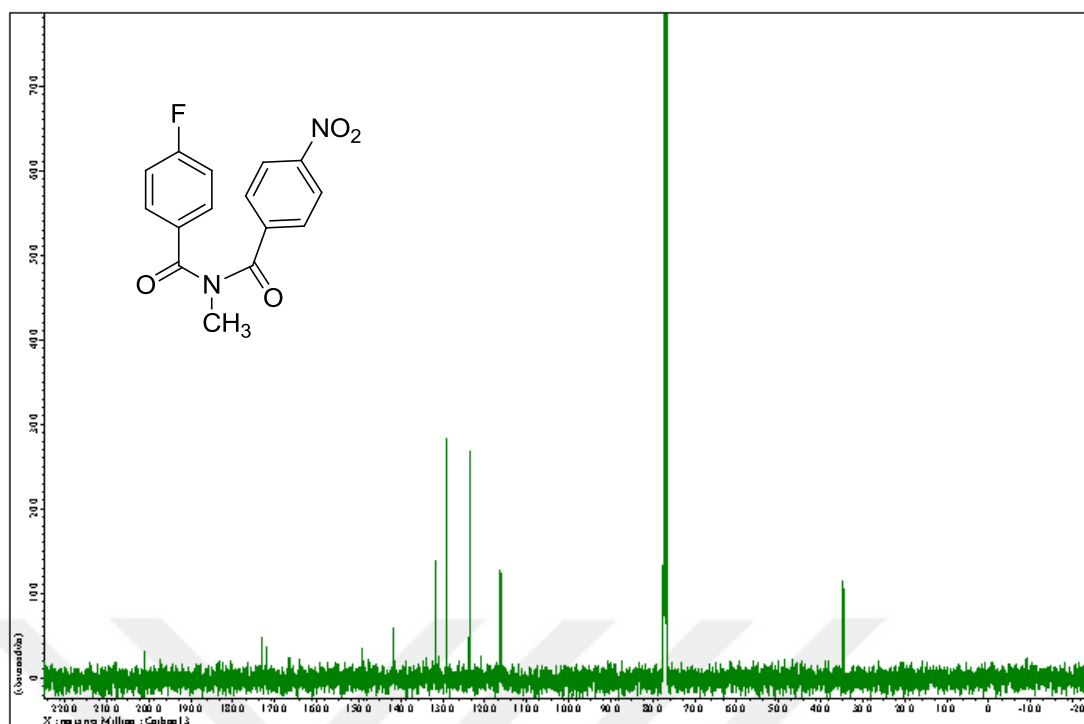


Figure A.87 ¹³C NMR Spectrum of compound **210d**

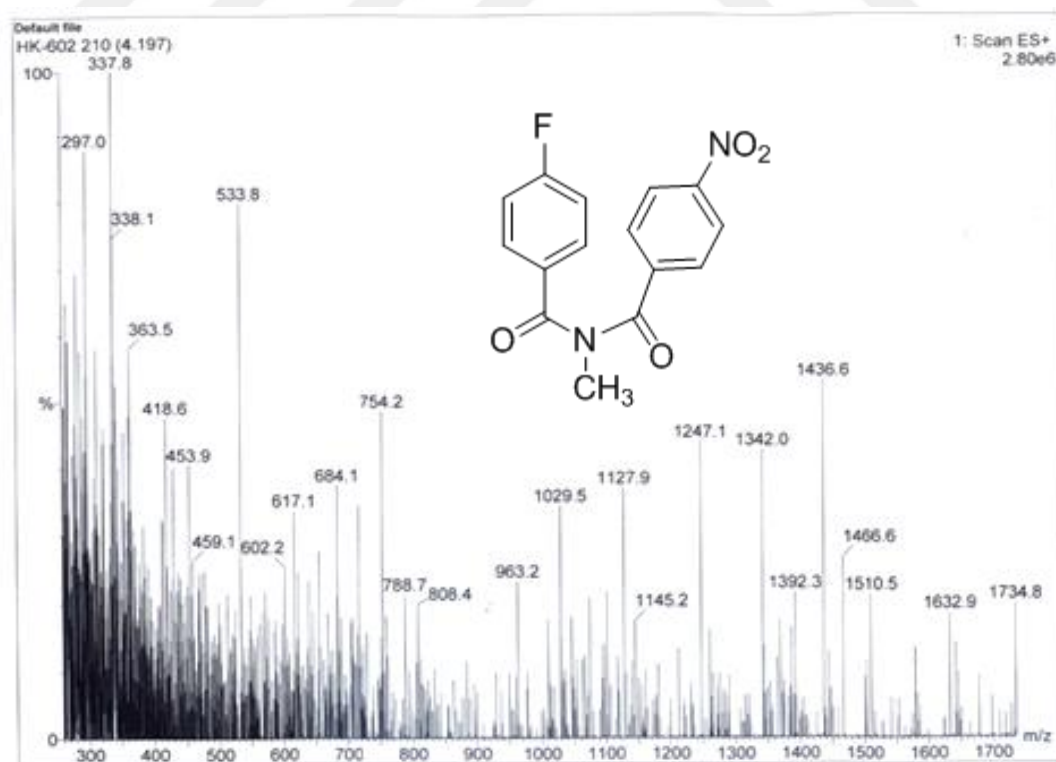


Figure A.88 MASS Spectrum of compound **210d**

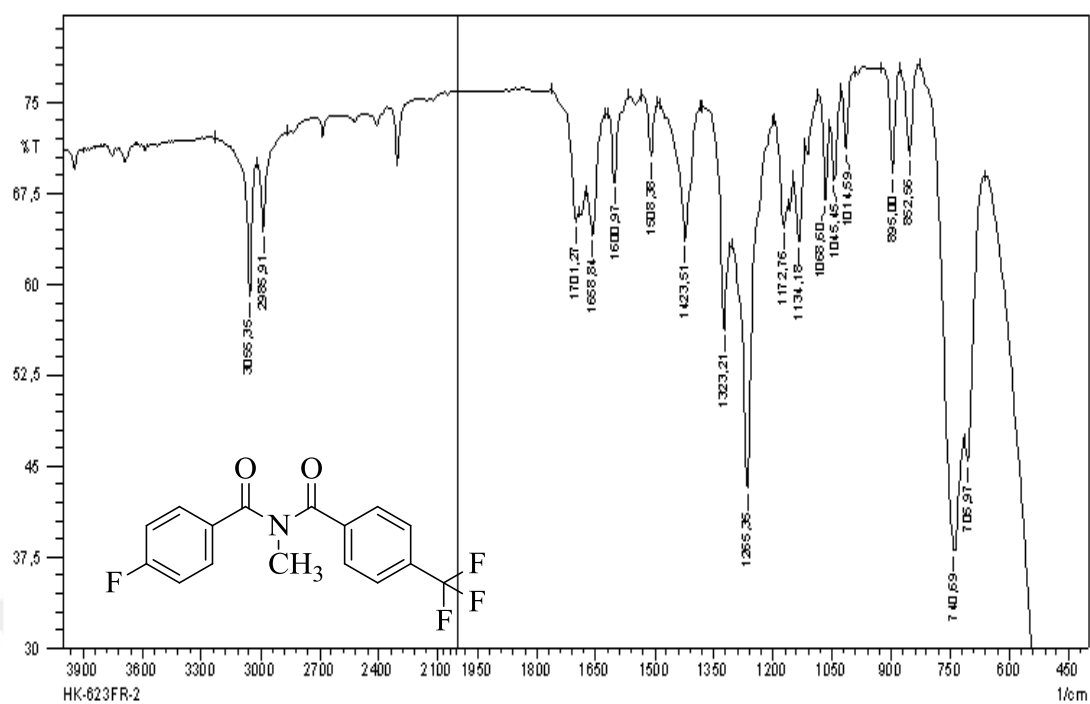


Figure A.89 IR Spectrum of compound **210f**

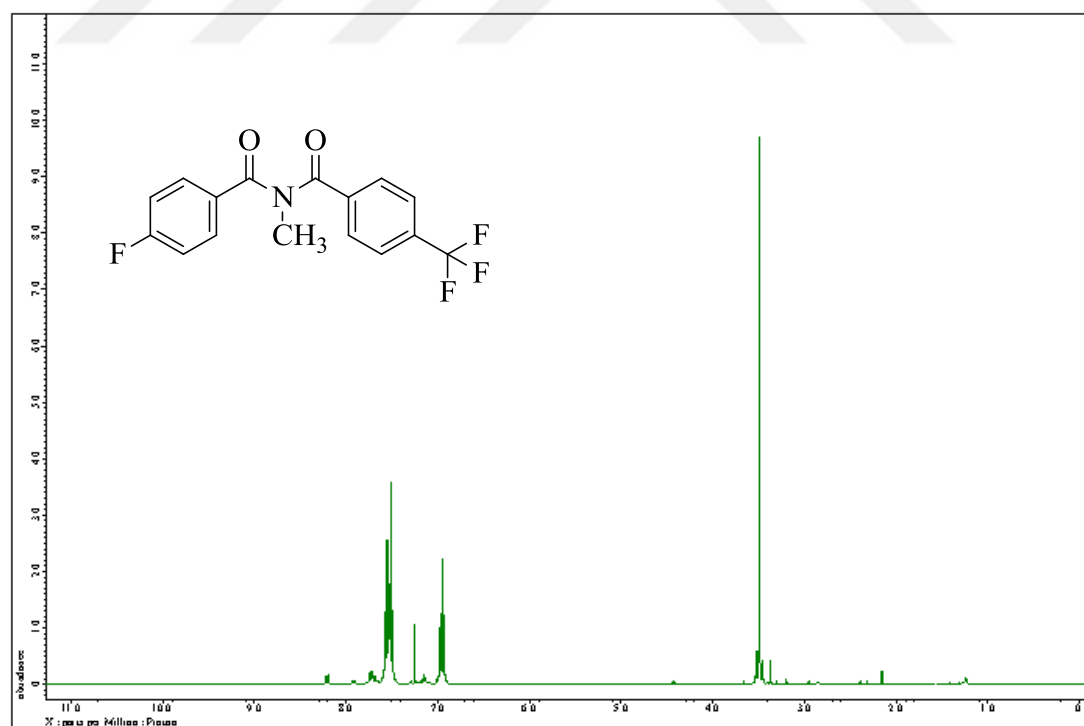


Figure A.90 ^1H NMR Spectrum of compound **210f**

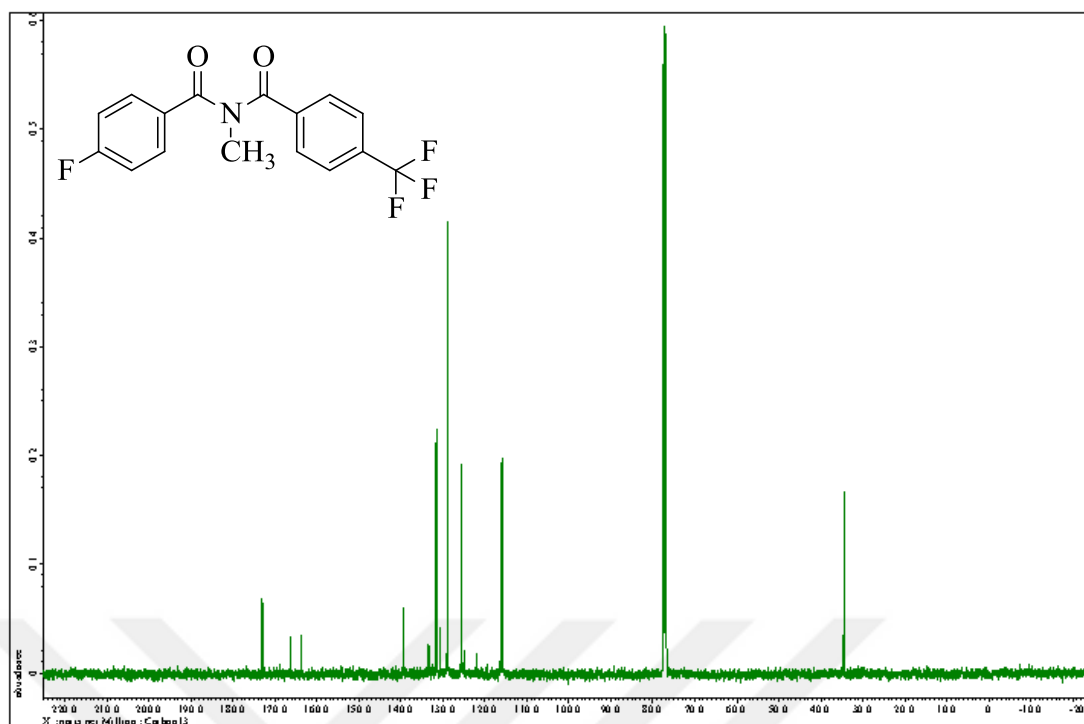


Figure A.91 ^{13}C NMR Spectrum of compound **210f**

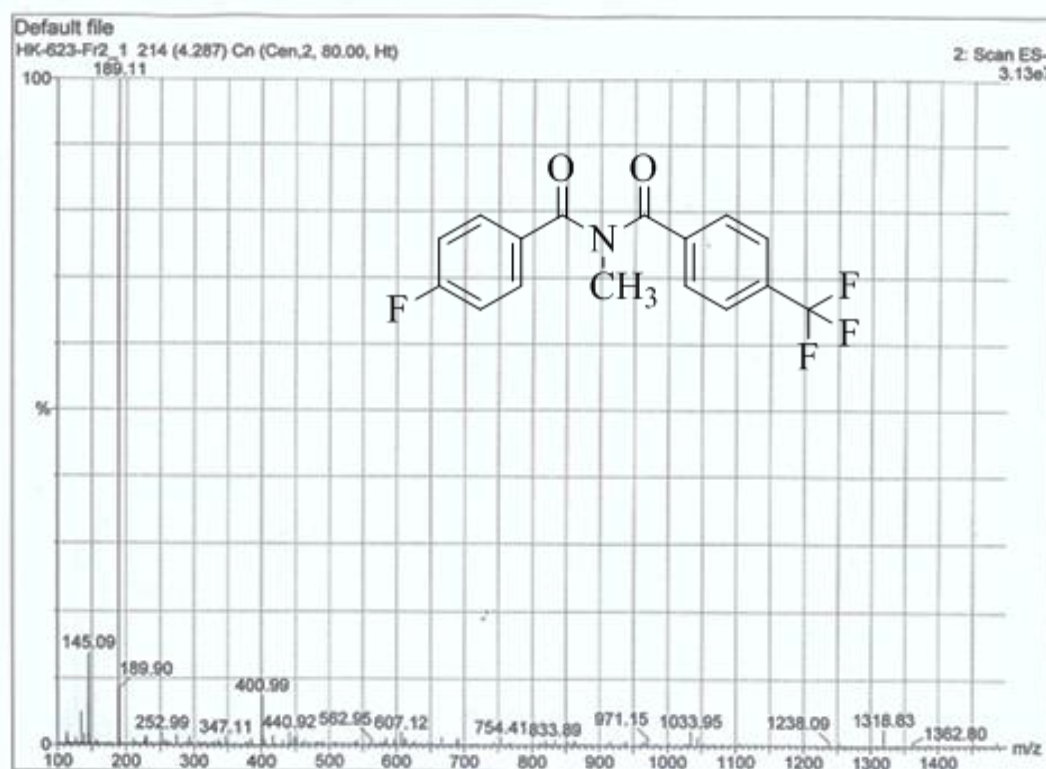


Figure A.92 MASS Spectrum of compound **210f**

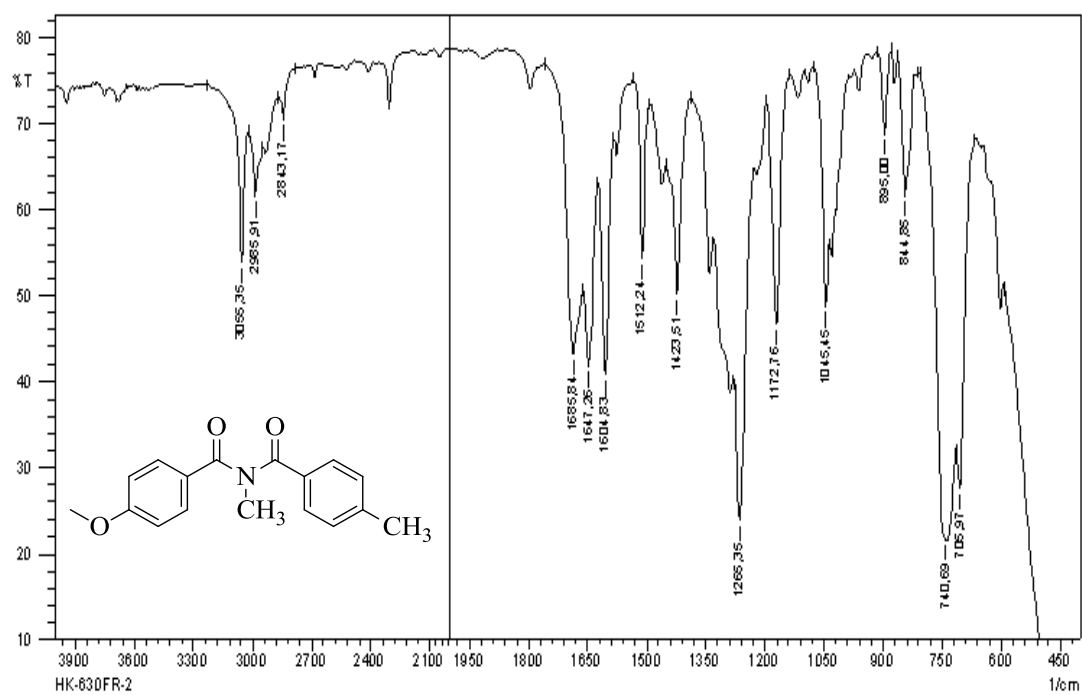


Figure A.93 IR Spectrum of compound **210h**

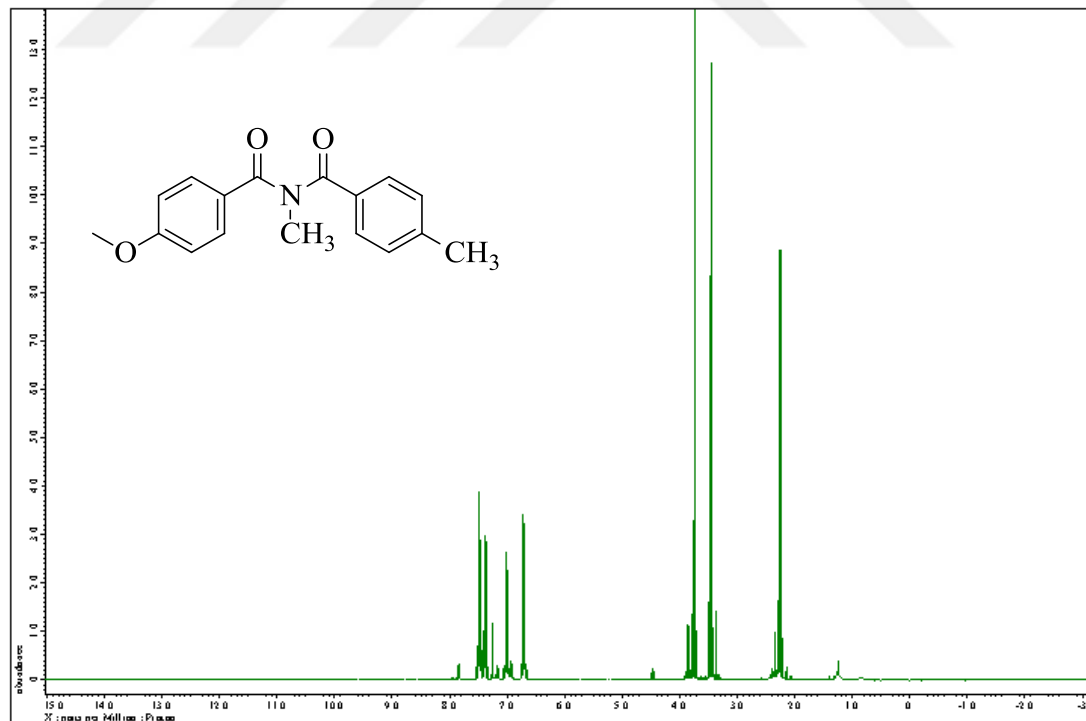


Figure A.94 ¹H NMR Spectrum of compound **210h**

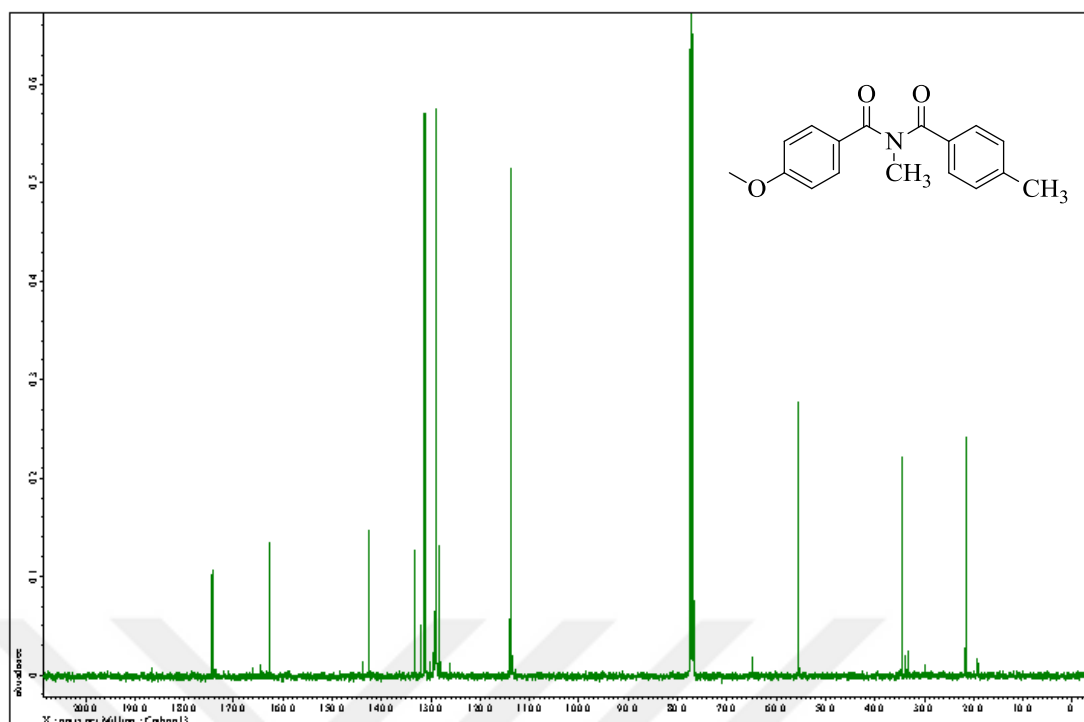


Figure A.95 ^{13}C NMR Spectrum of compound **210h**

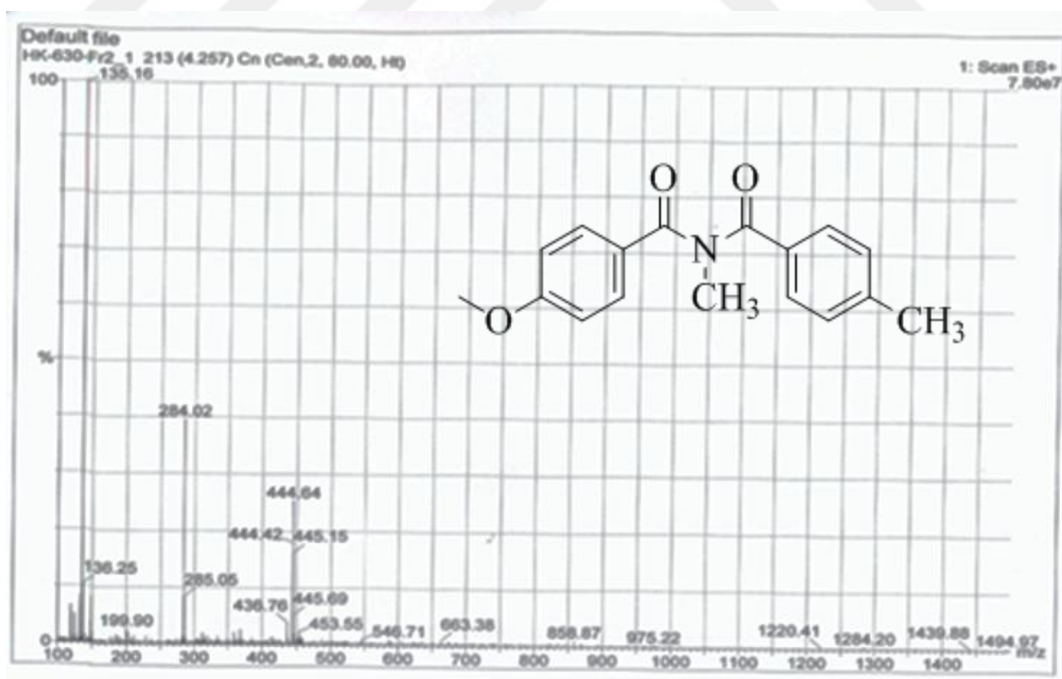


Figure A.96 MASS Spectrum of compound **210h**

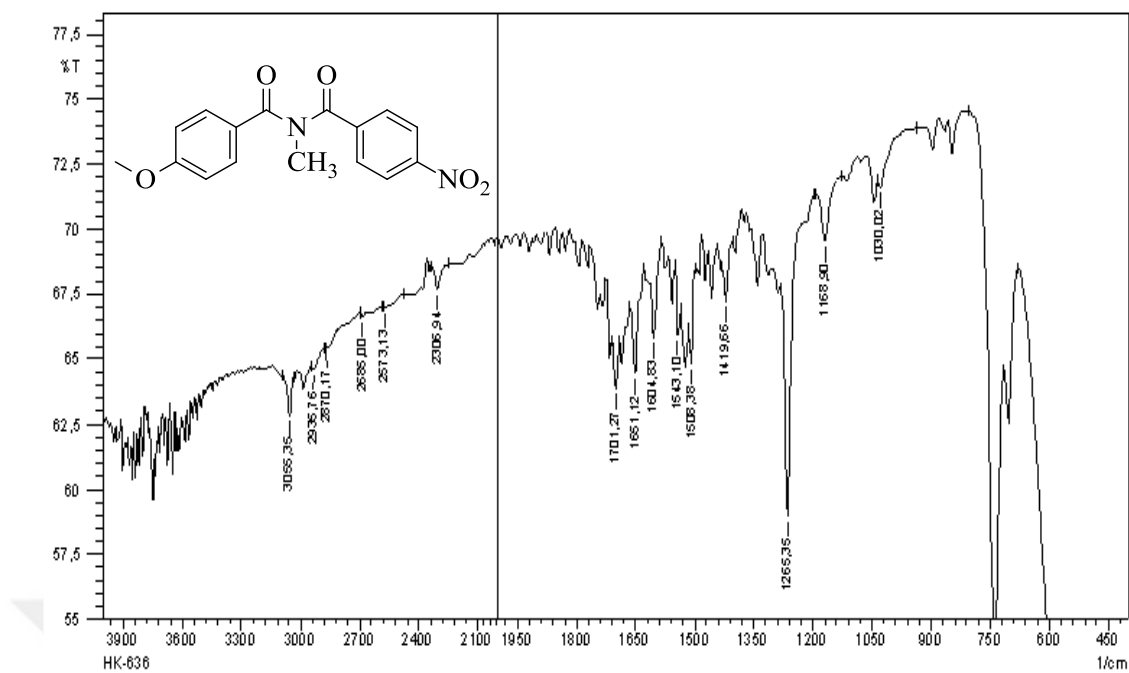


Figure A.97 IR Spectrum of compound **210i**

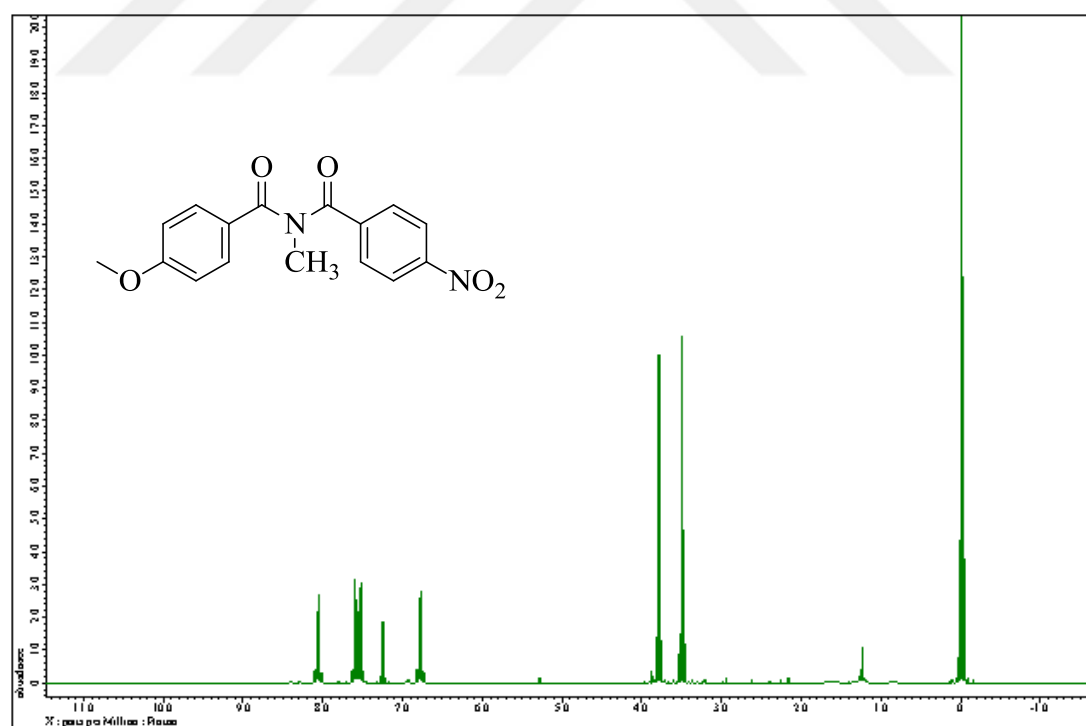


Figure A.98 ^1H NMR Spectrum of compound **210i**

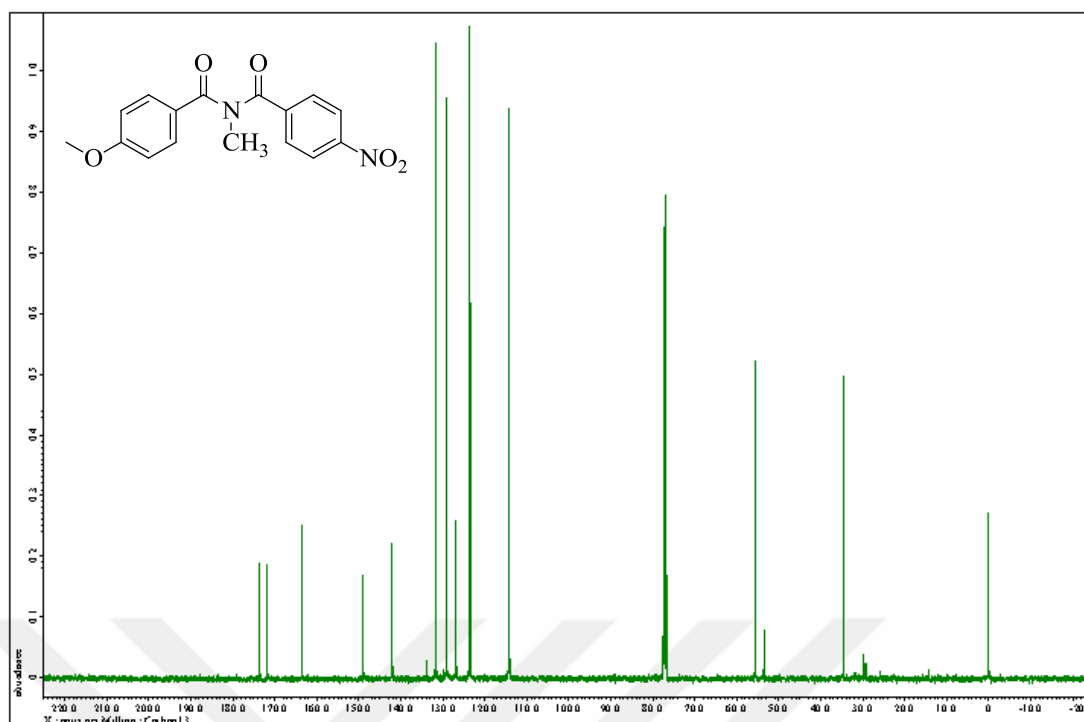


Figure A.99 ^{13}C NMR Spectrum of compound **210i**

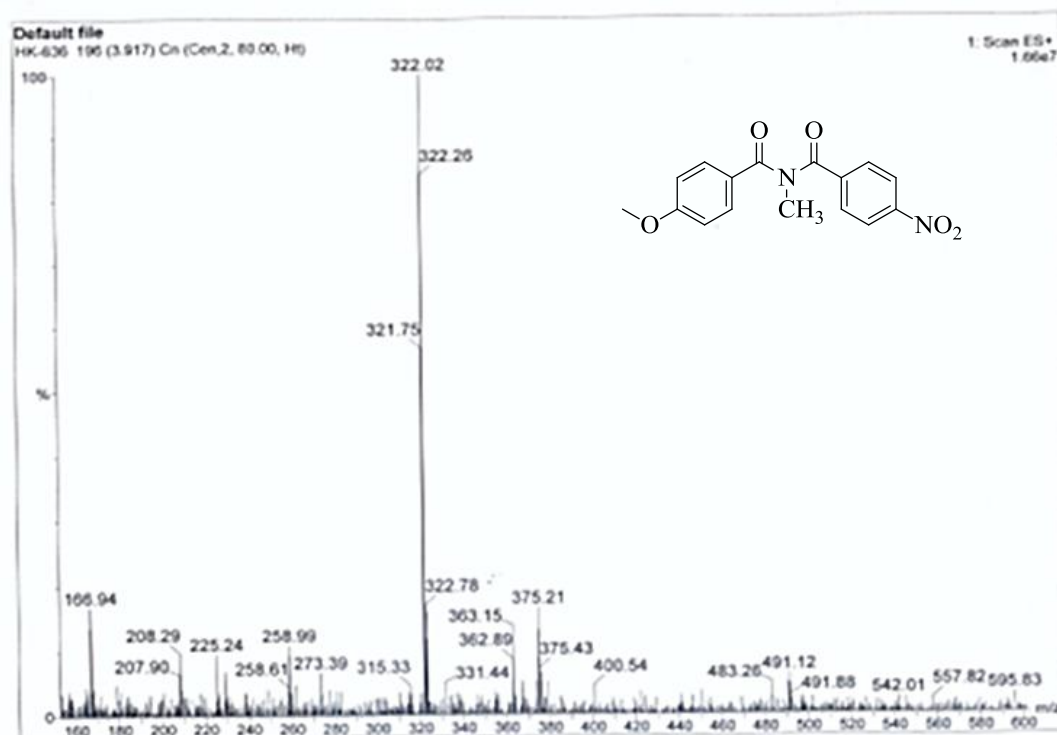


Figure A.100 MASS Spectrum of compound **210i**

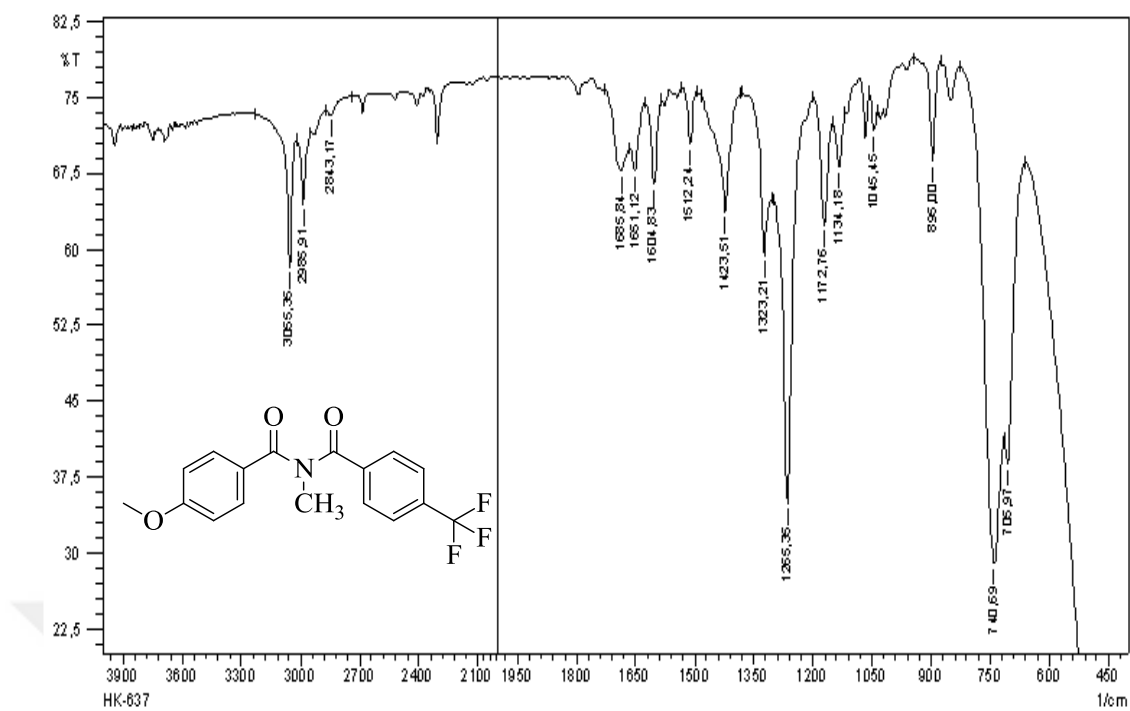


Figure A.101 IR Spectrum of compound 210j

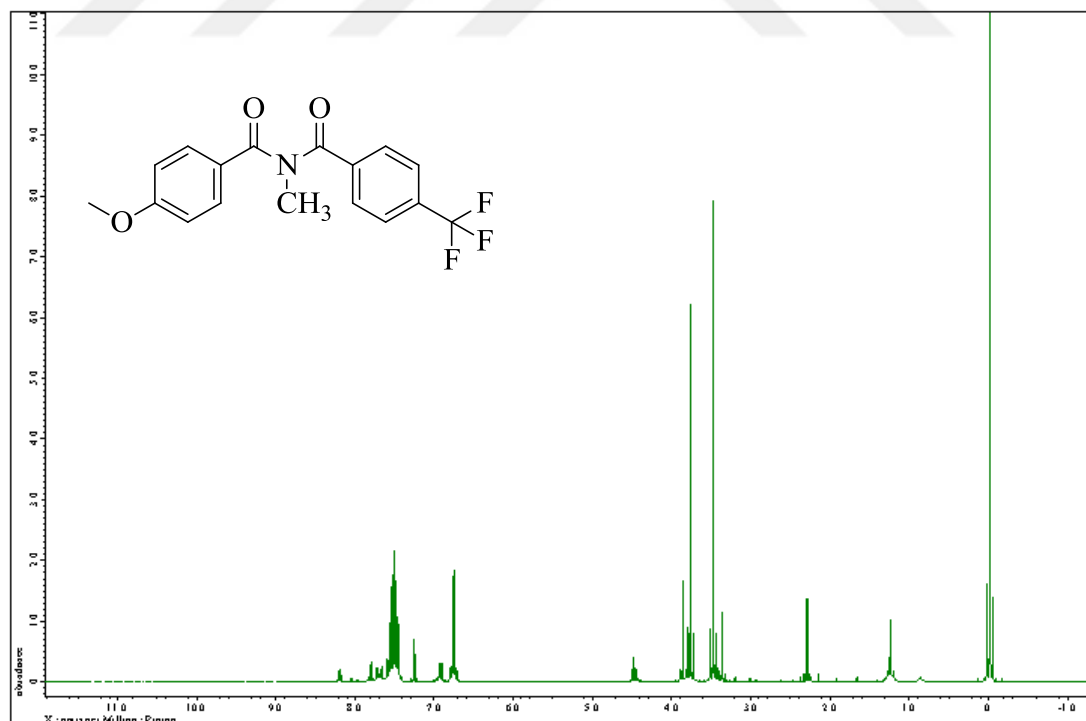


Figure A.102 ¹H NMR Spectrum of compound 210j

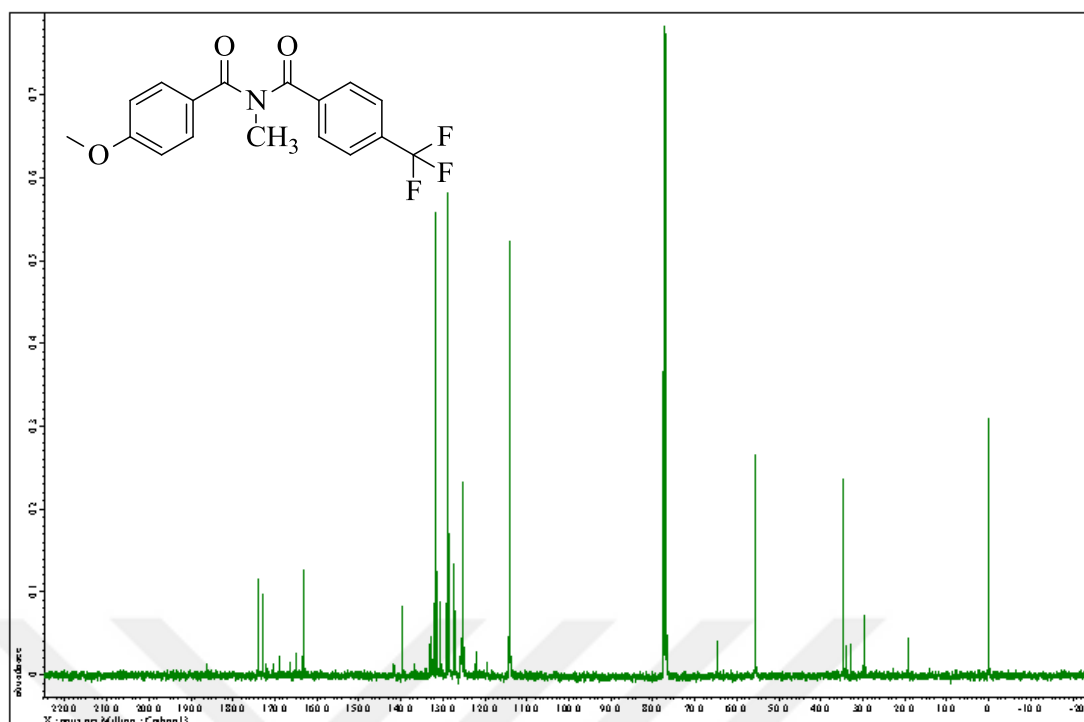


Figure A.103 ¹³C NMR Spectrum of compound 210j

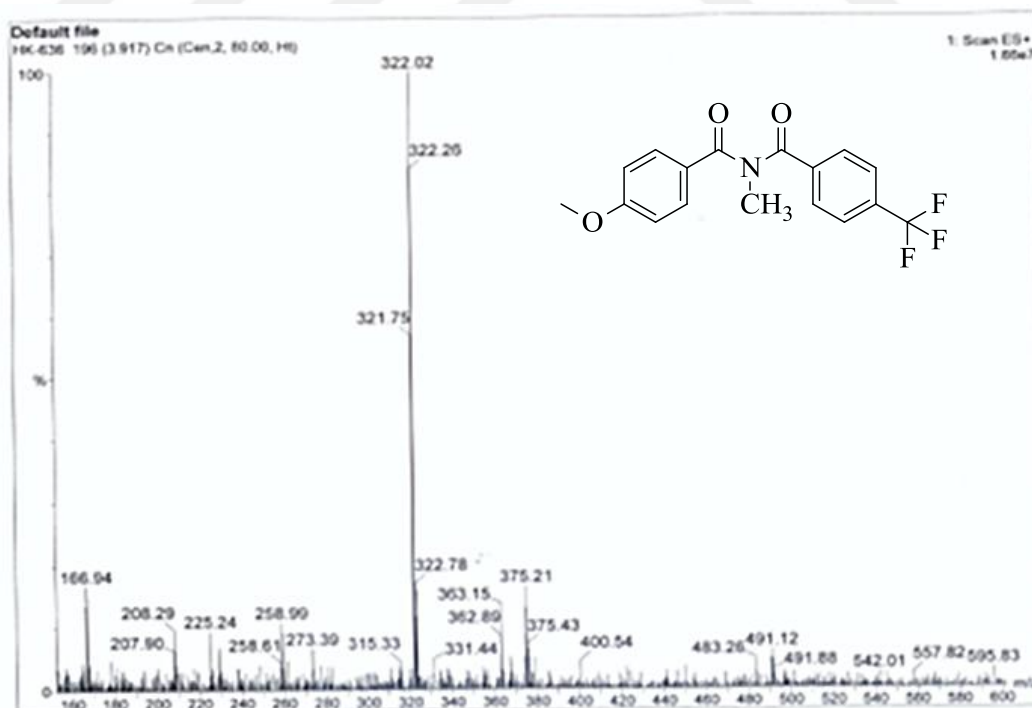


Figure A.104 MASS Spectrum of compound 210j

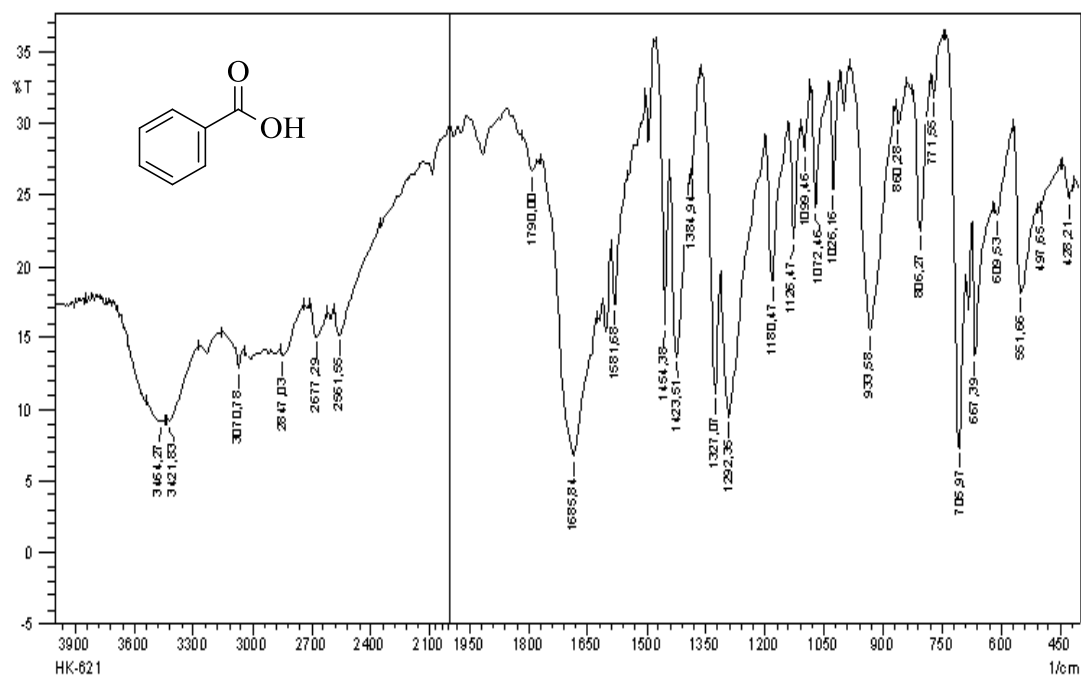


Figure A.105 IR Spectrum of compound **211a**

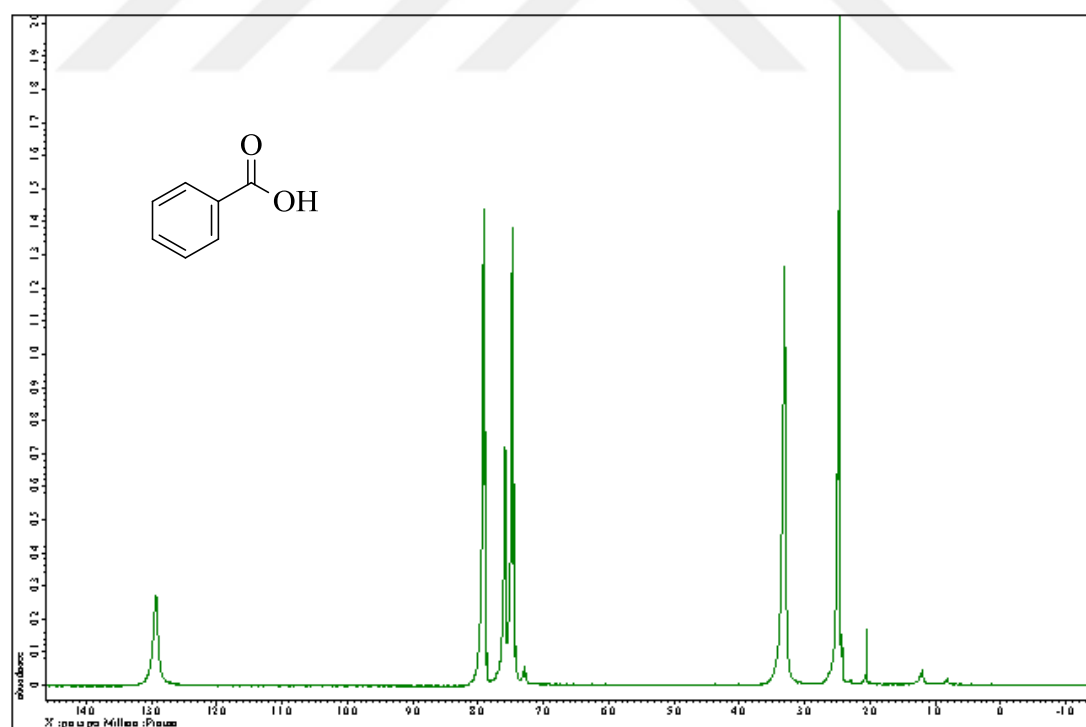


Figure A.106 ^1H NMR Spectrum of compound **211a**

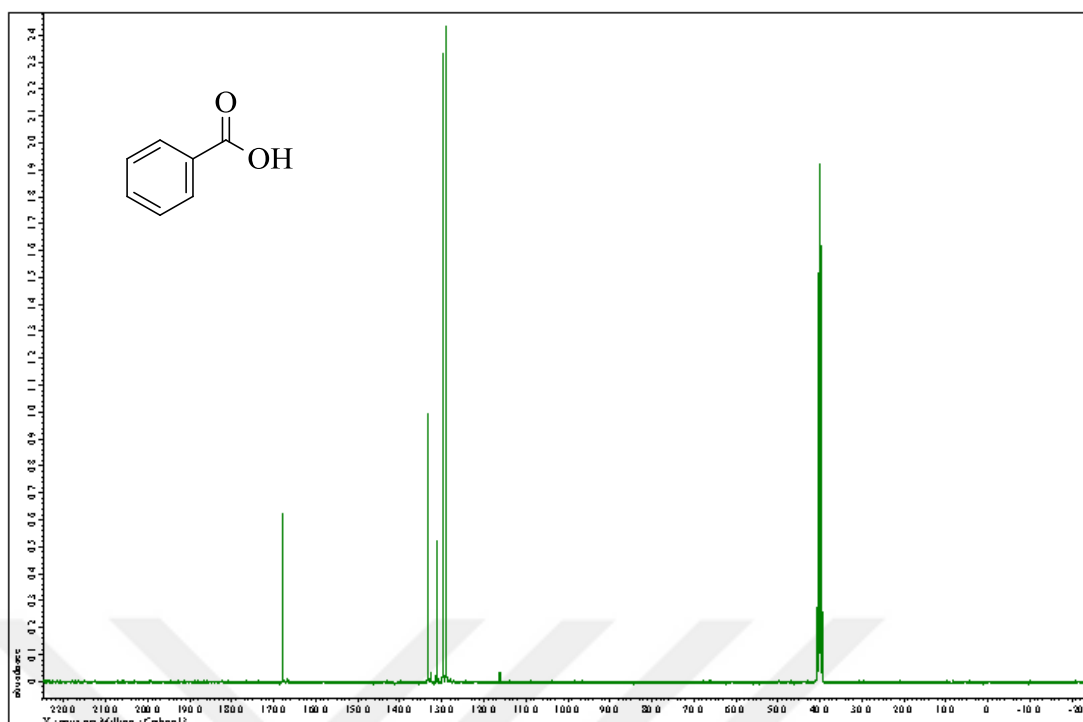


Figure A.107 ^{13}C NMR Spectrum of compound 211a

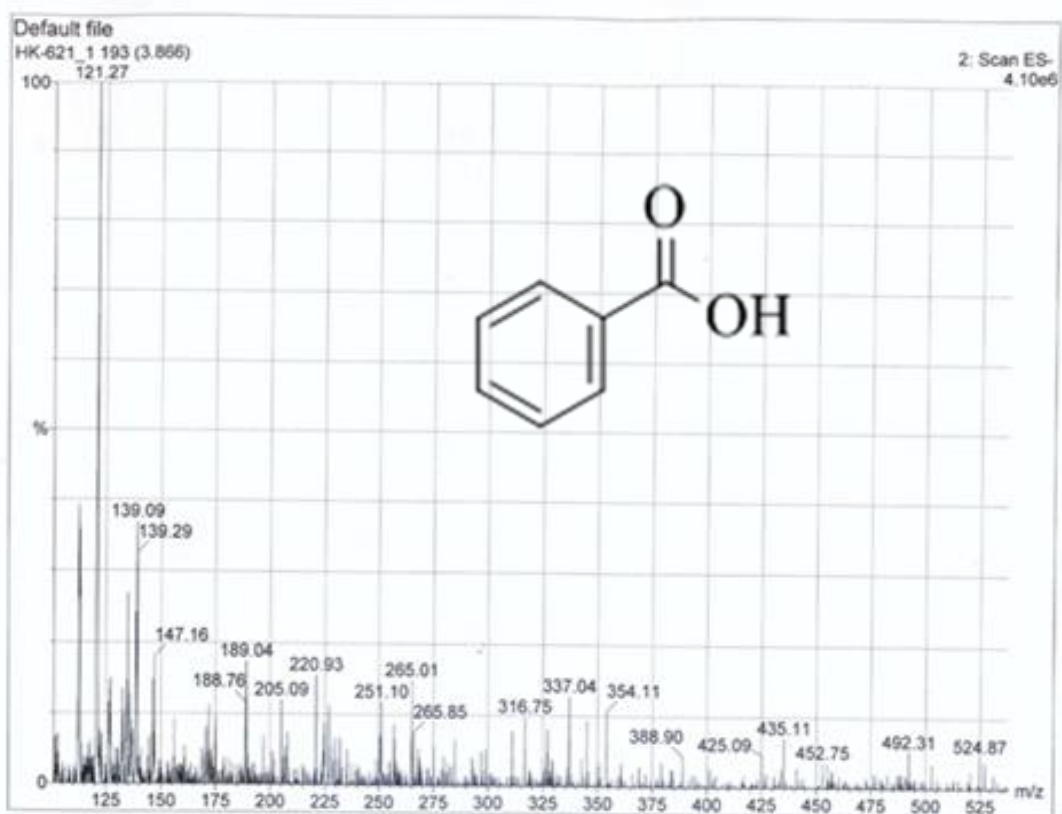


Figure A.108 MASS Spectrum of compound 211a

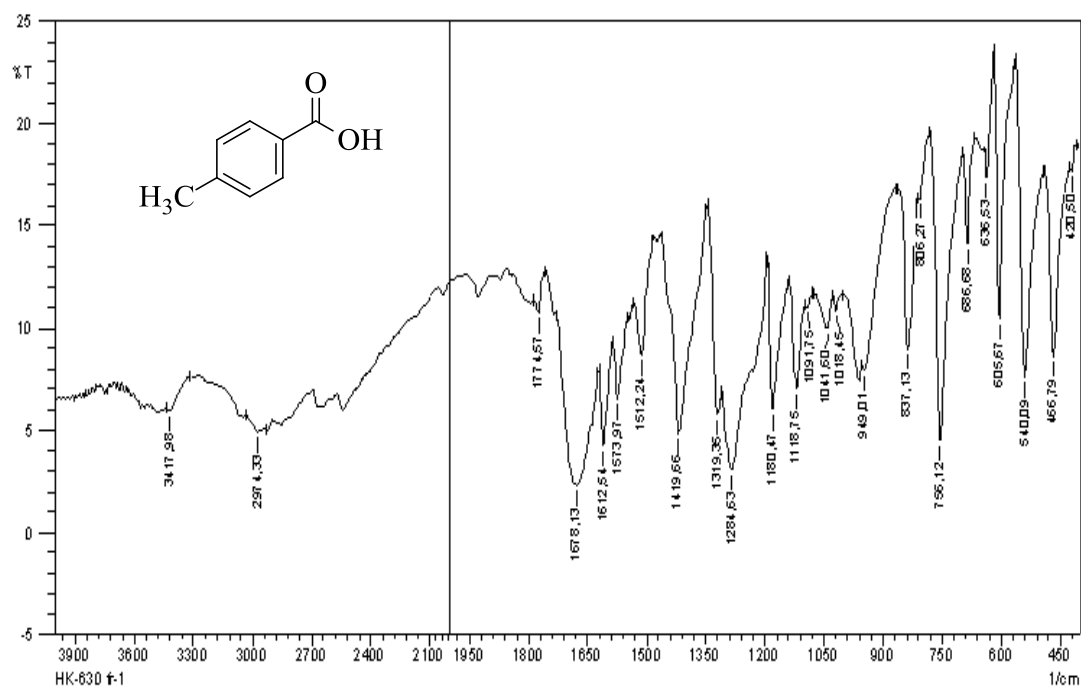


Figure A.109 IR Spectrum of compound **211b**

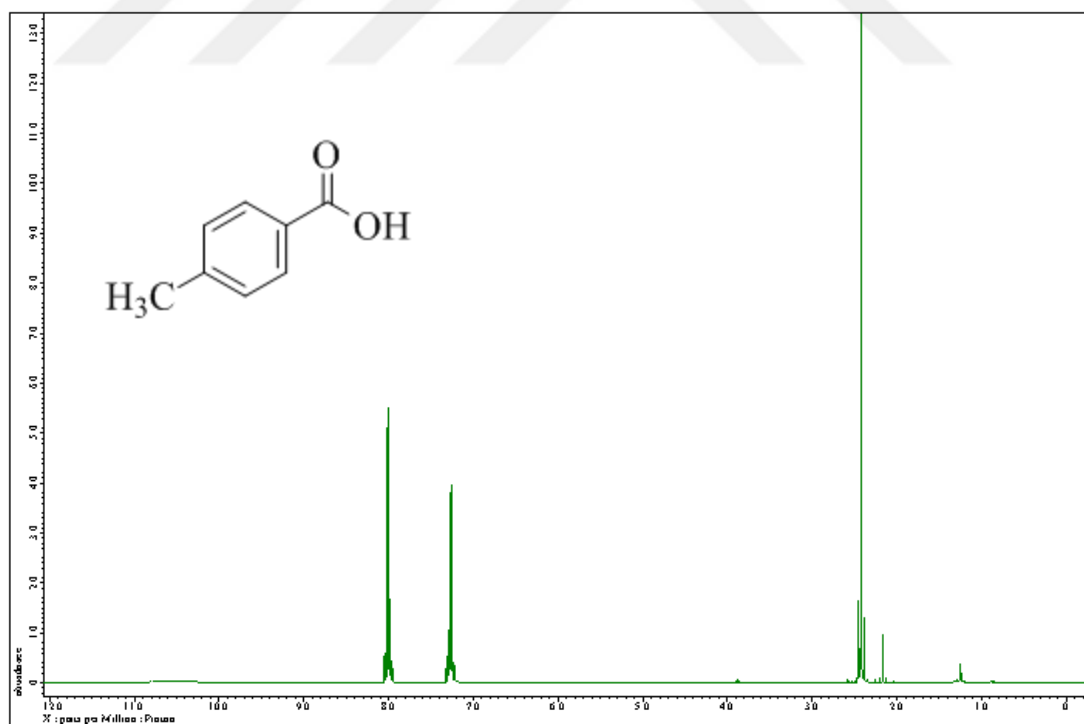


Figure A.110 ¹H NMR Spectrum of compound **211b**

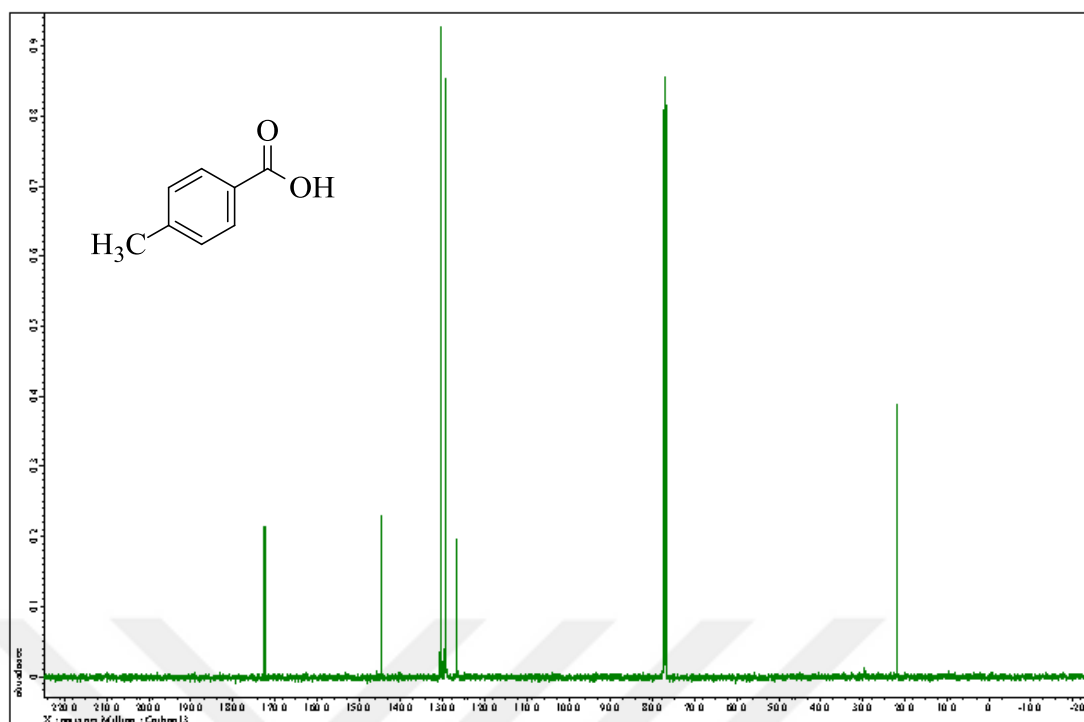


Figure A.111 ¹³C NMR Spectrum of compound 211b

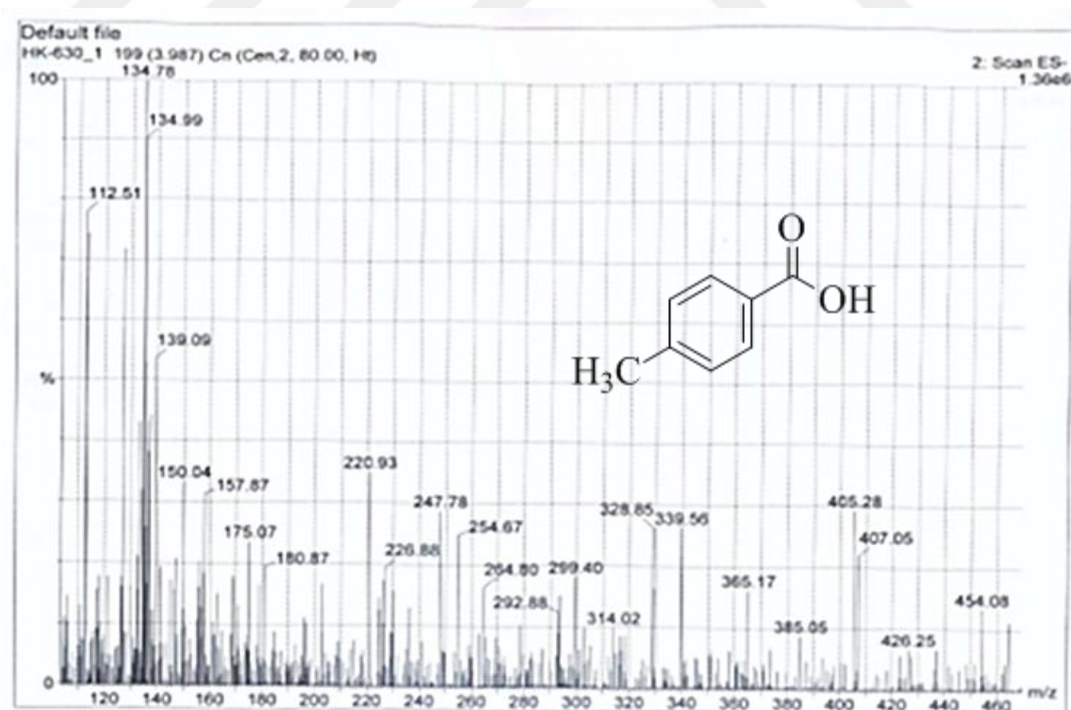


Figure A.112 MASS Spectrum of compound 211b

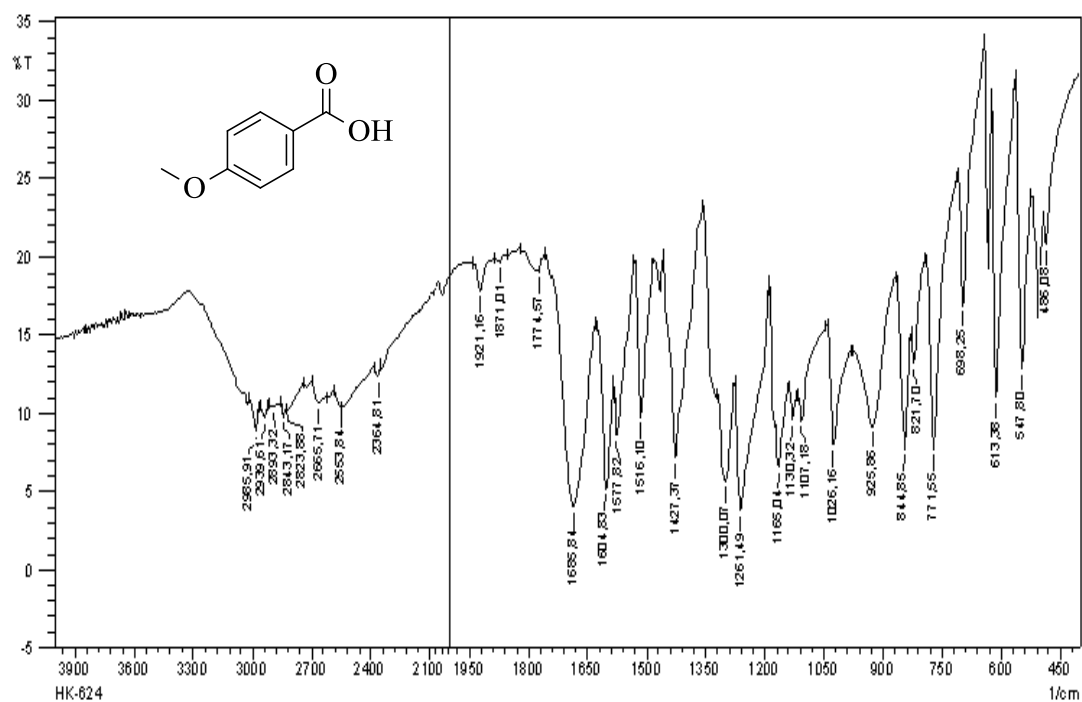


Figure A.113 IR Spectrum of compound **211c**

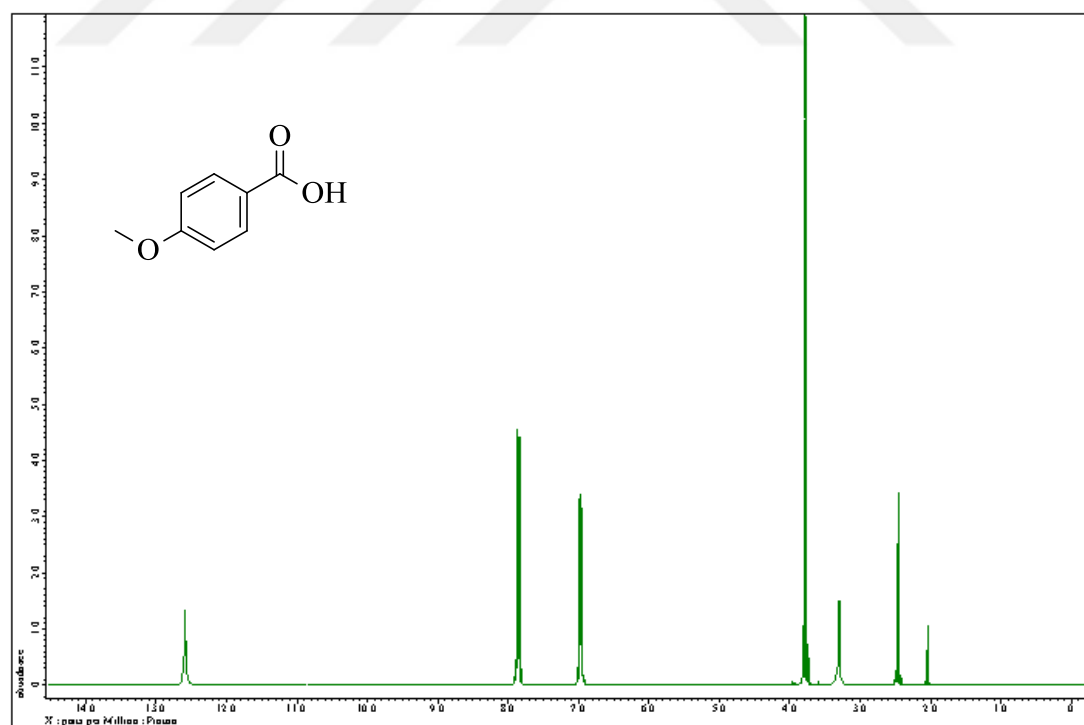


Figure A.114 ¹H NMR Spectrum of compound **211c**

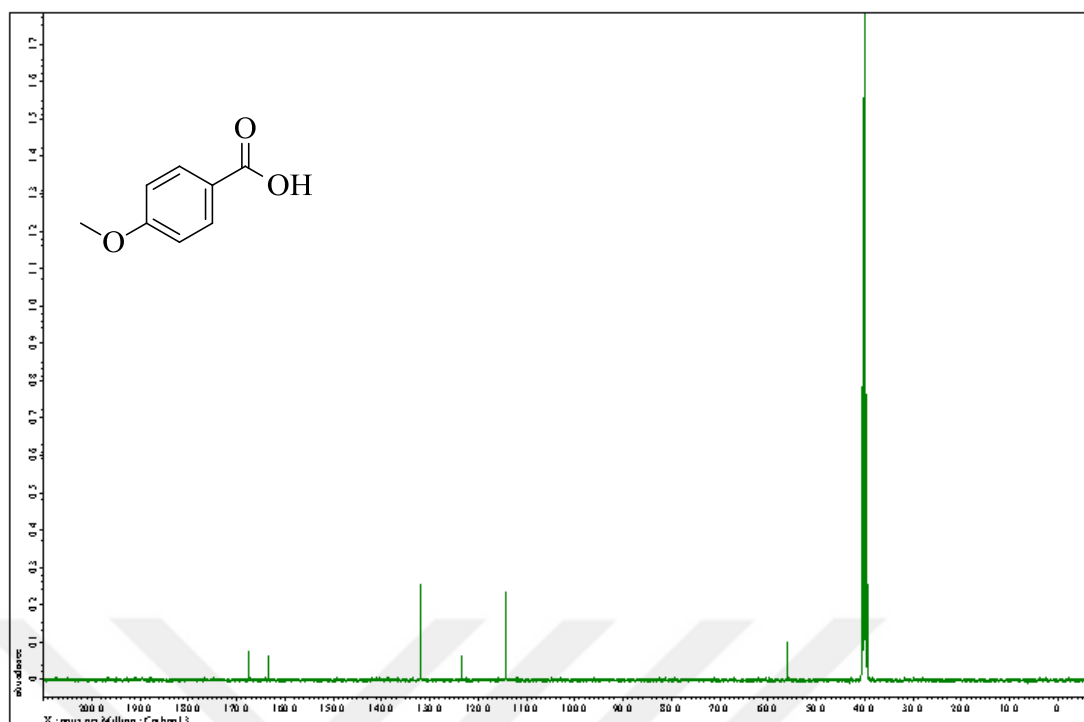


Figure A.115 ^{13}C NMR Spectrum of compound 211c

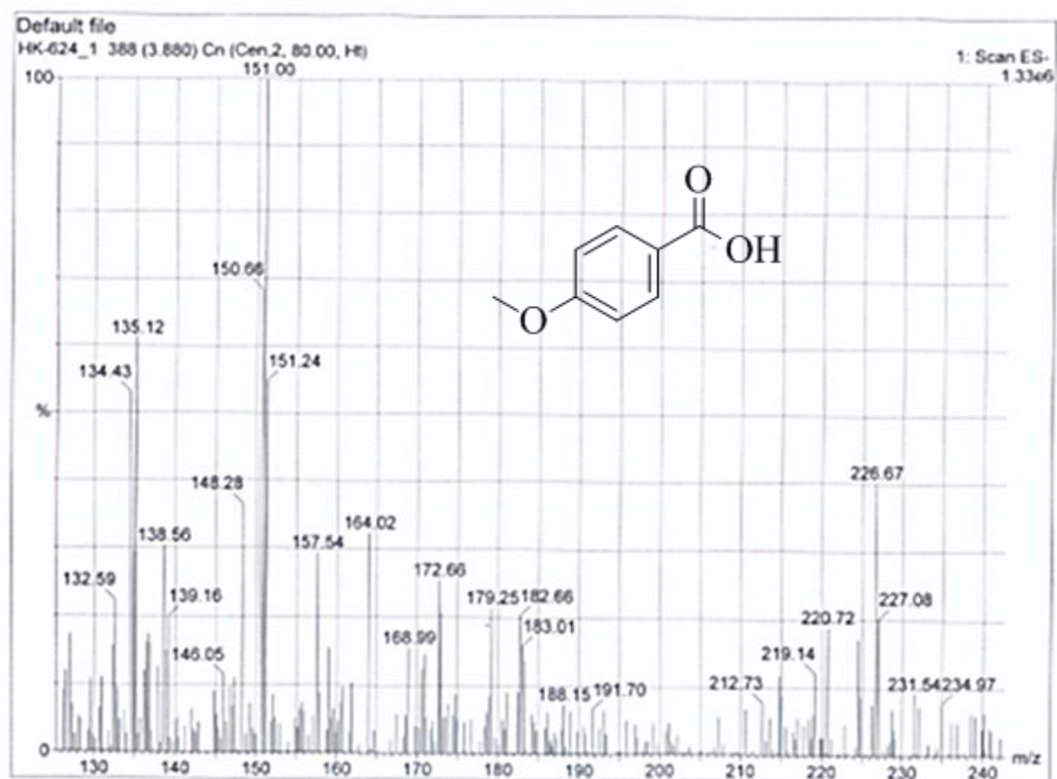


Figure A.116 MASS Spectrum of compound 211c

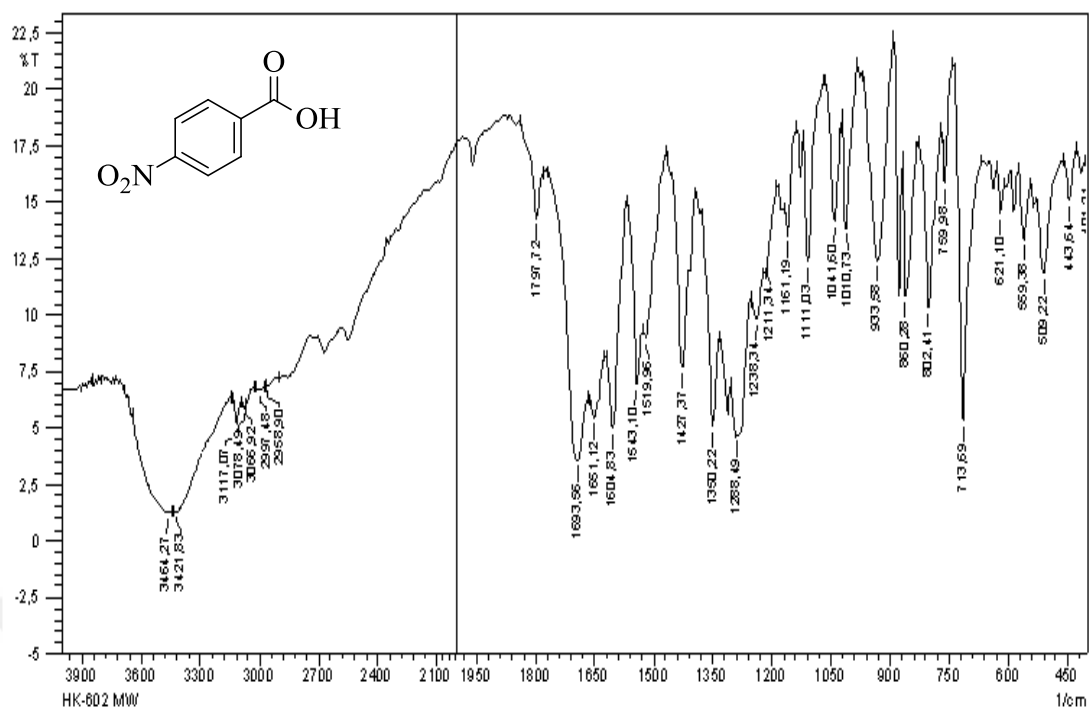


Figure A.117 IR Spectrum of compound **211d**

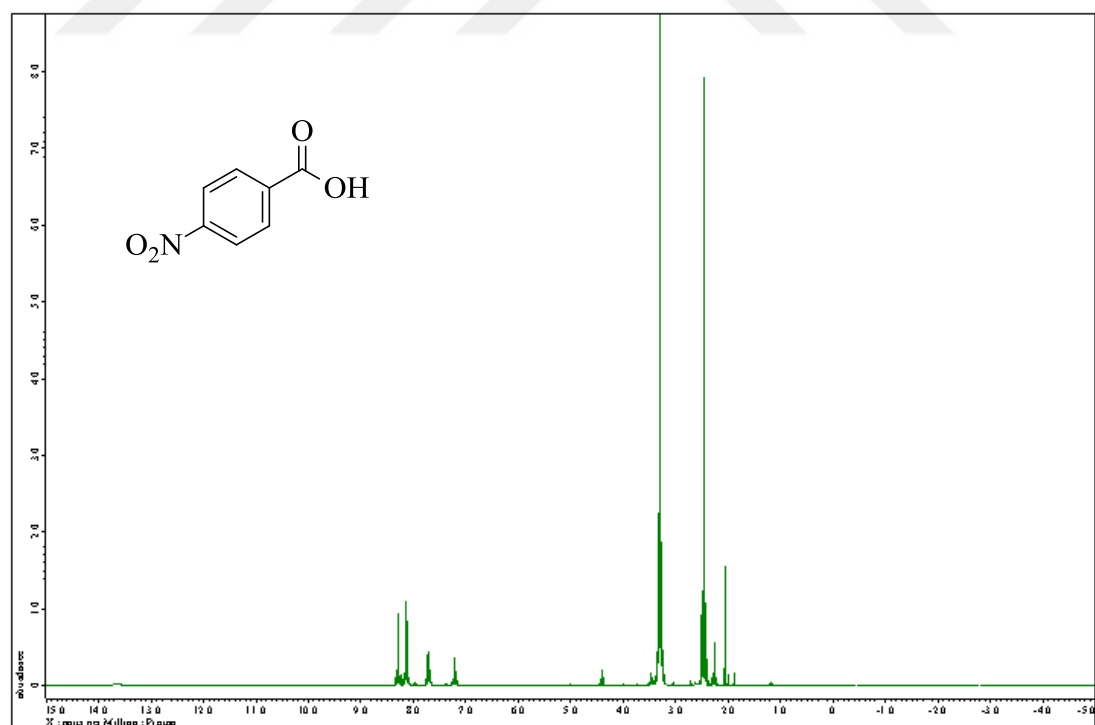


Figure A.118 ^1H NMR Spectrum of compound **211d**

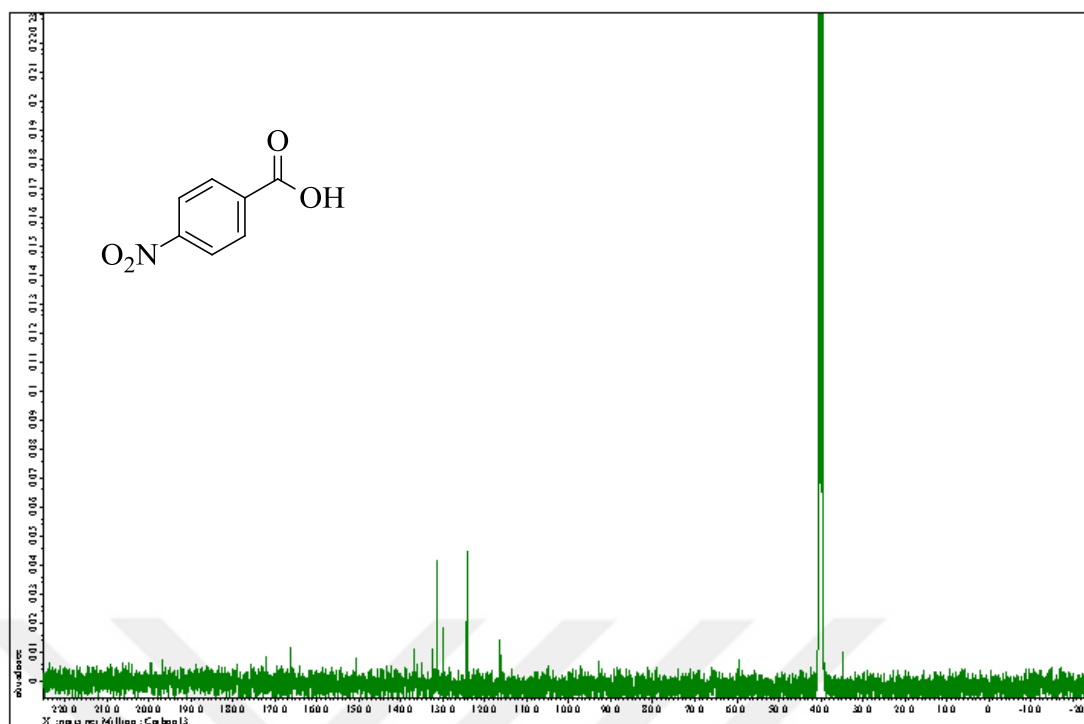


Figure A.119 ^{13}C NMR Spectrum of compound **211d**

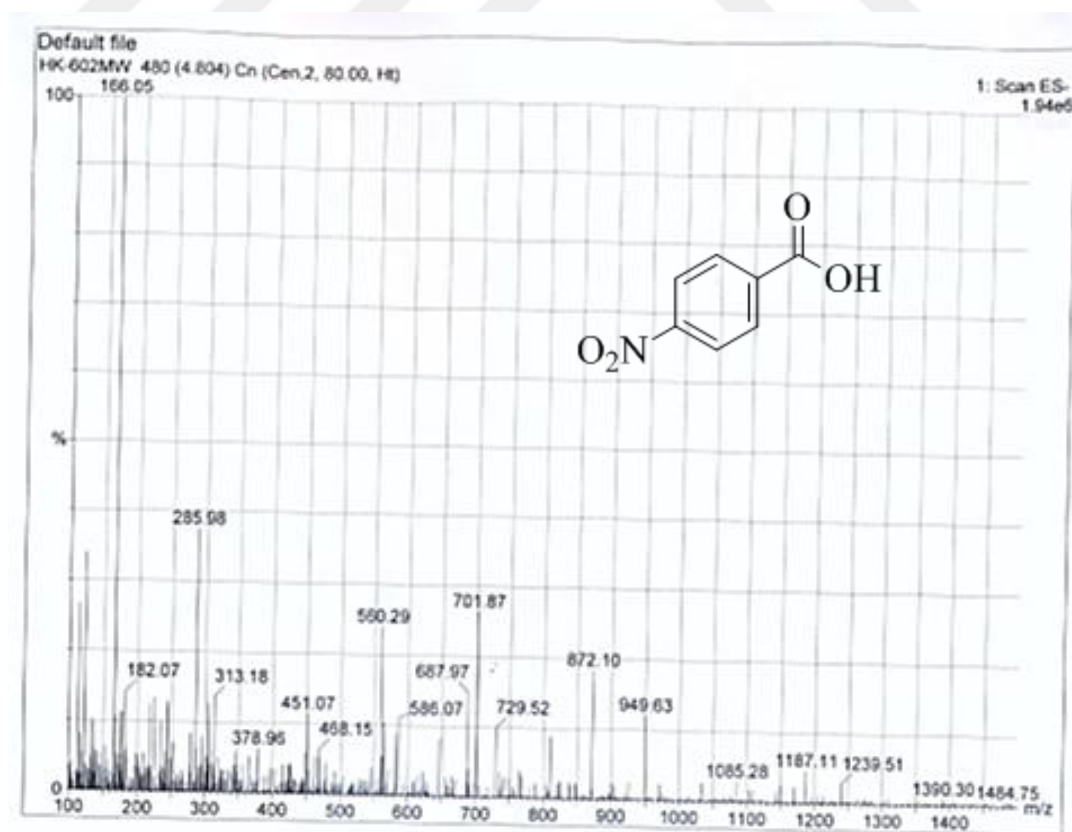


Figure A.120 MASS Spectrum of compound **211d**

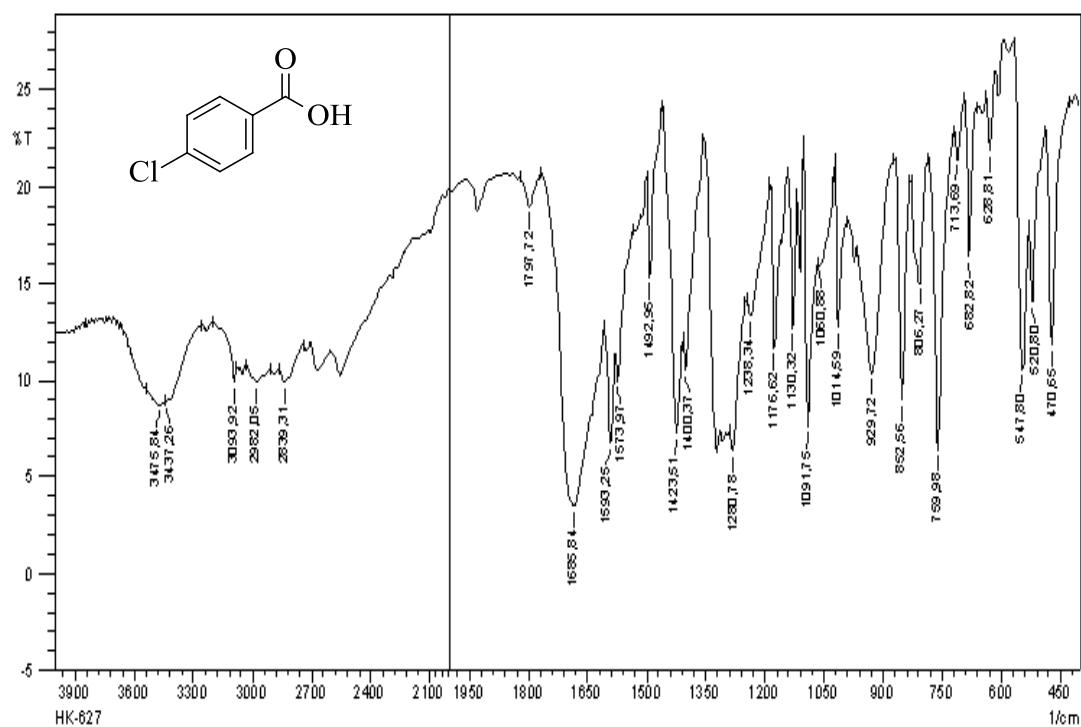


Figure A.121 IR Spectrum of compound **211e**

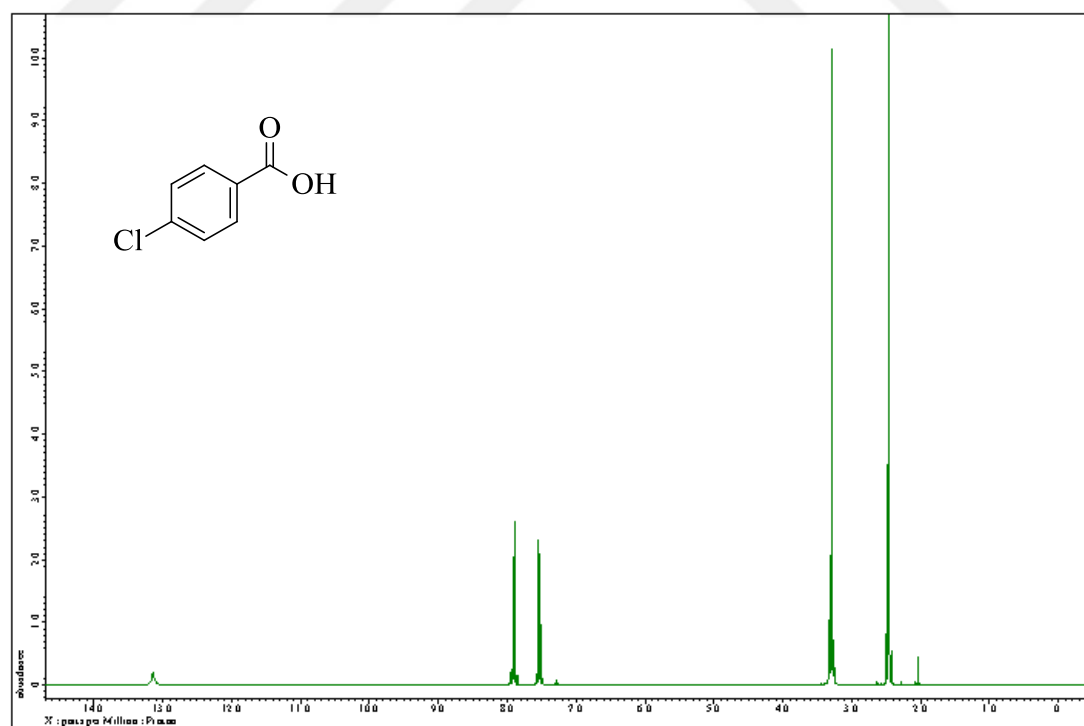


Figure A.122 ¹H NMR Spectrum of compound **211e**

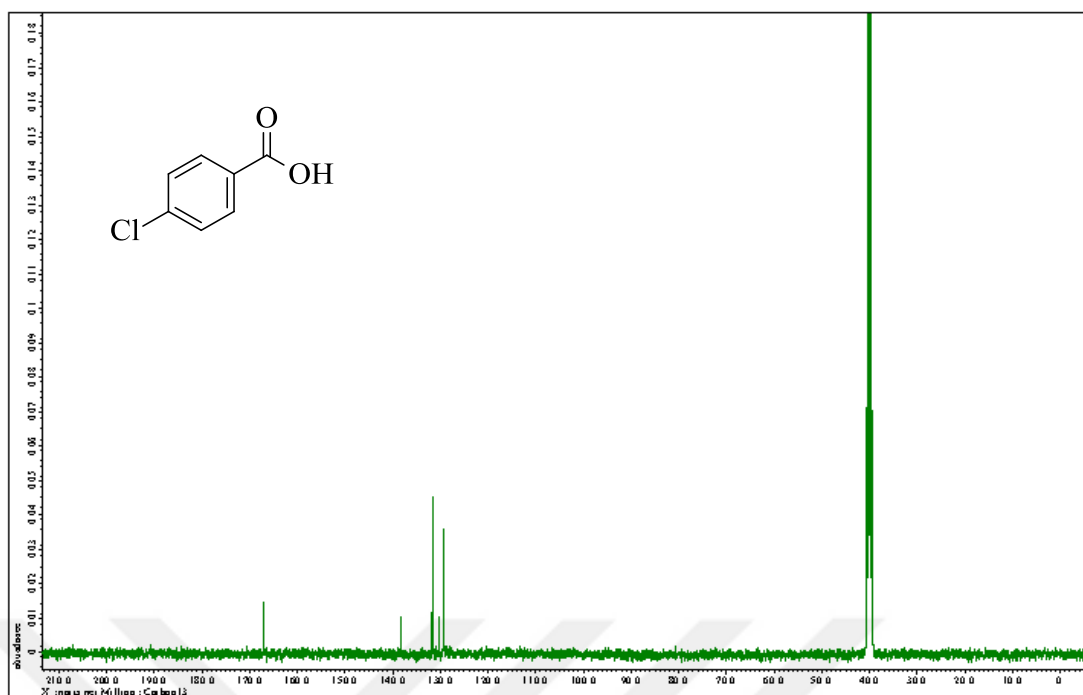


Figure A.123 ¹³C NMR Spectrum of compound 211e

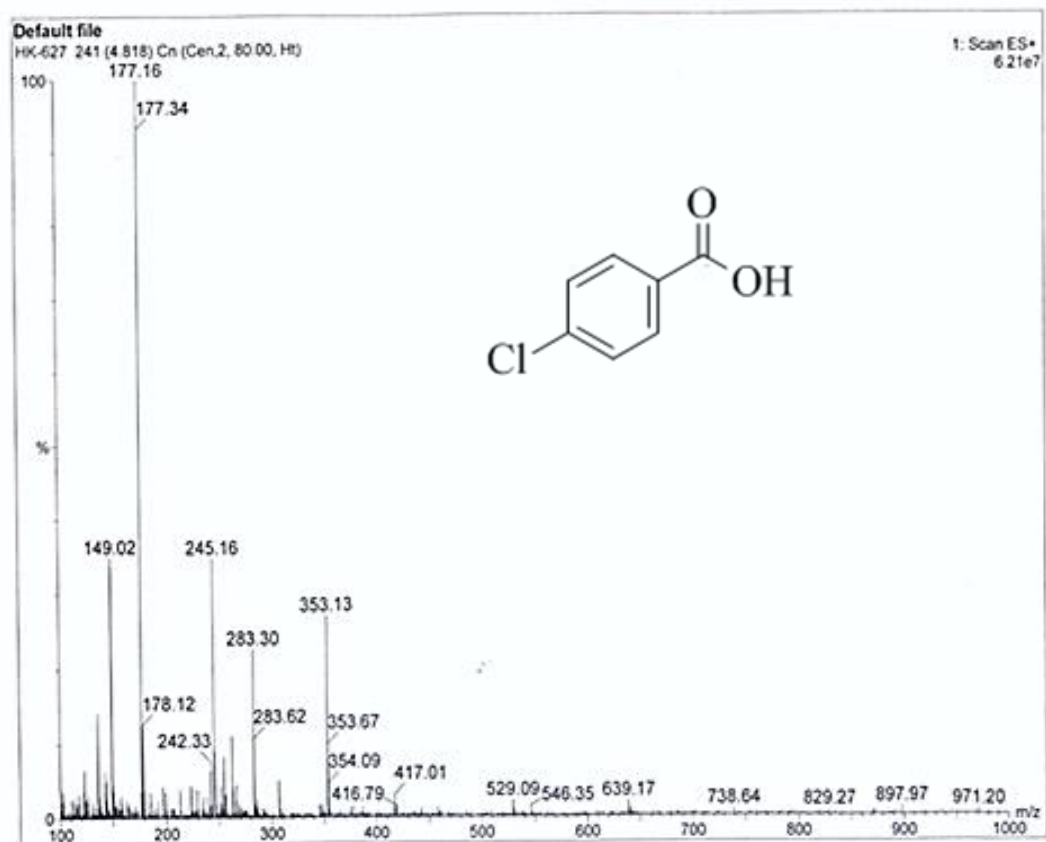


Figure A.124 MASS Spectrum of compound 211e

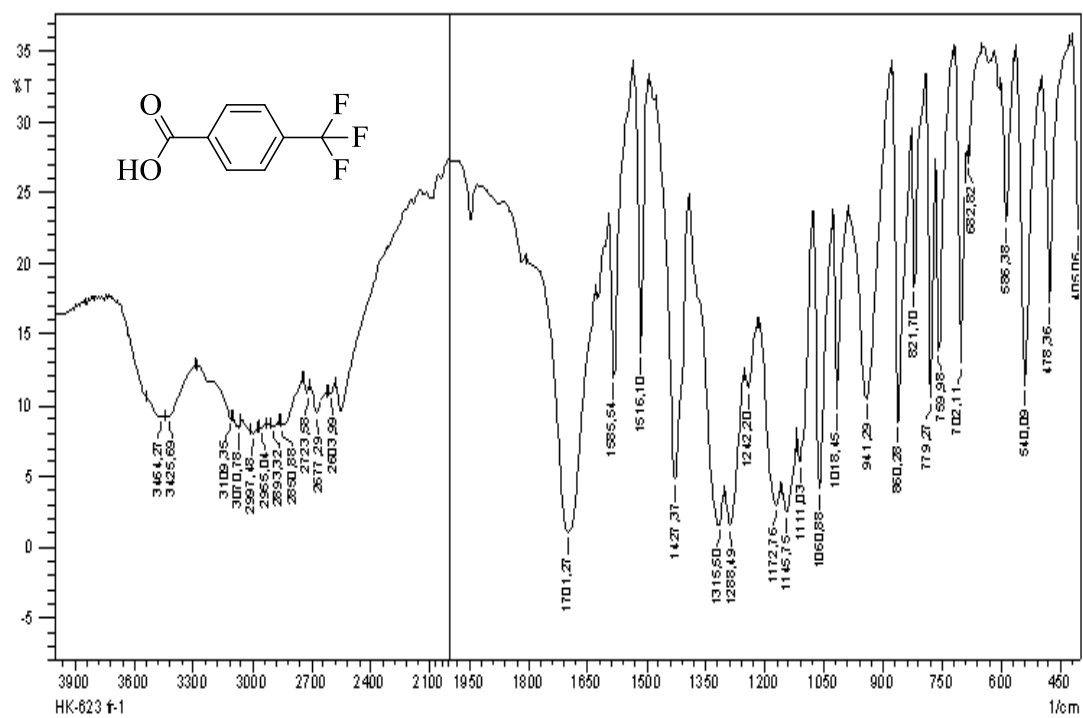


Figure A.125 IR Spectrum of compound 211f

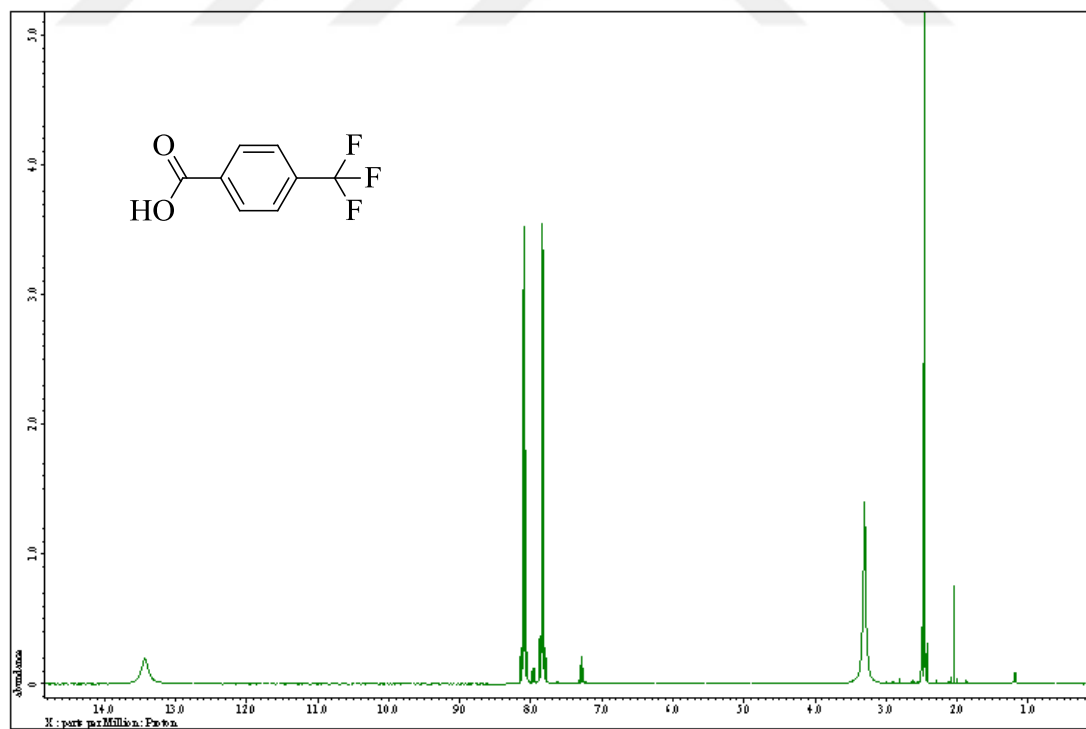


Figure A.126 ¹H NMR Spectrum of compound 211f

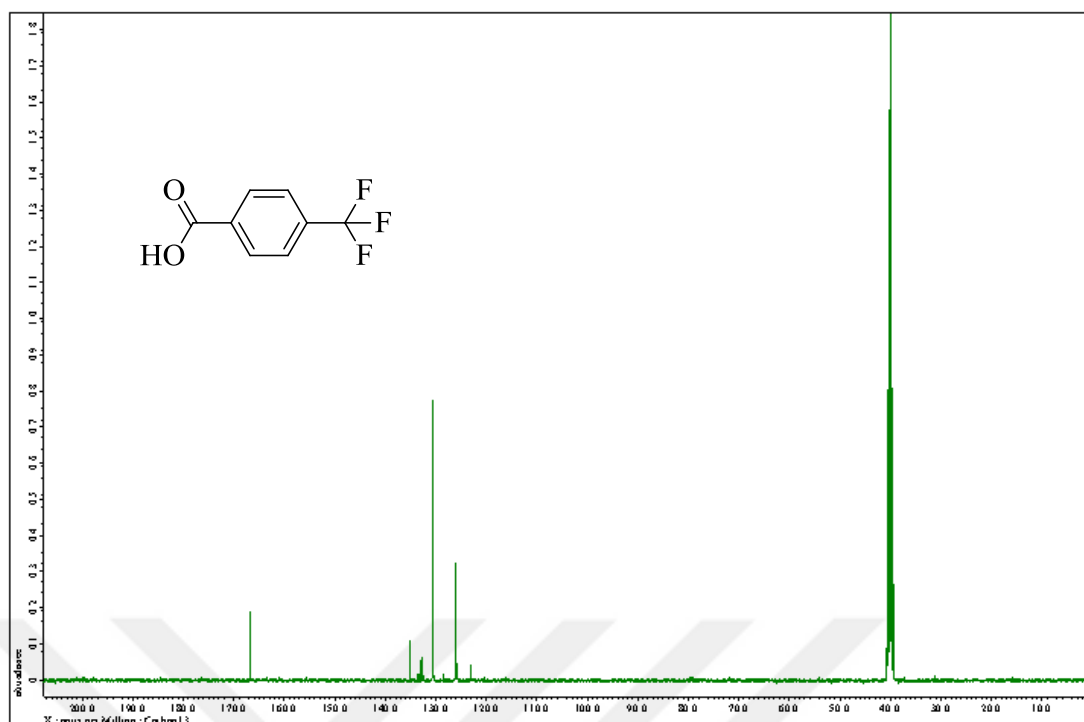


Figure A.127 ^{13}C NMR Spectrum of compound **211f**

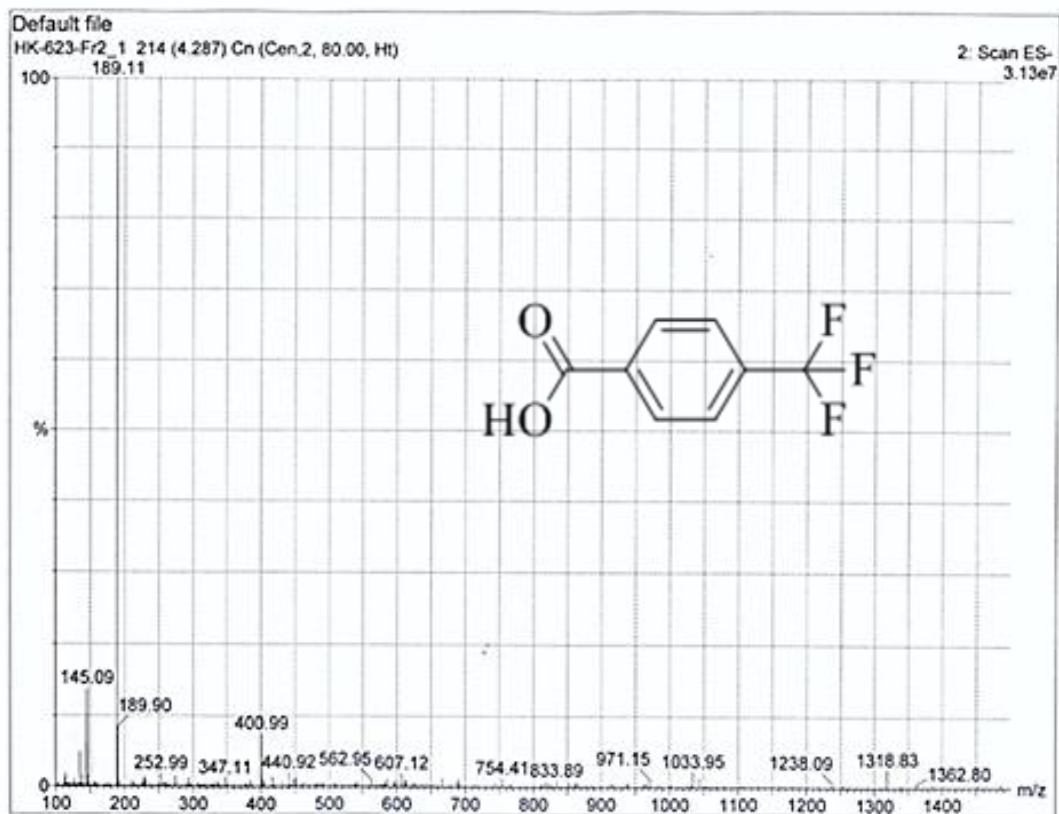


Figure A.128 MASS Spectrum of compound **211f**

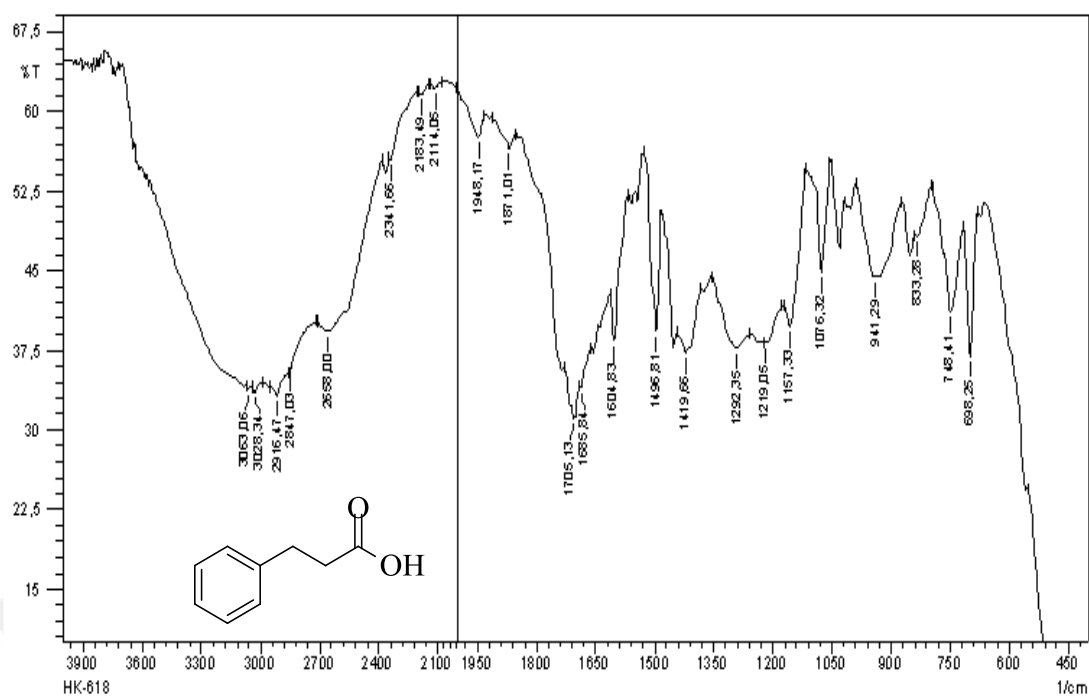


Figure A.129 IR Spectrum of compound 211g

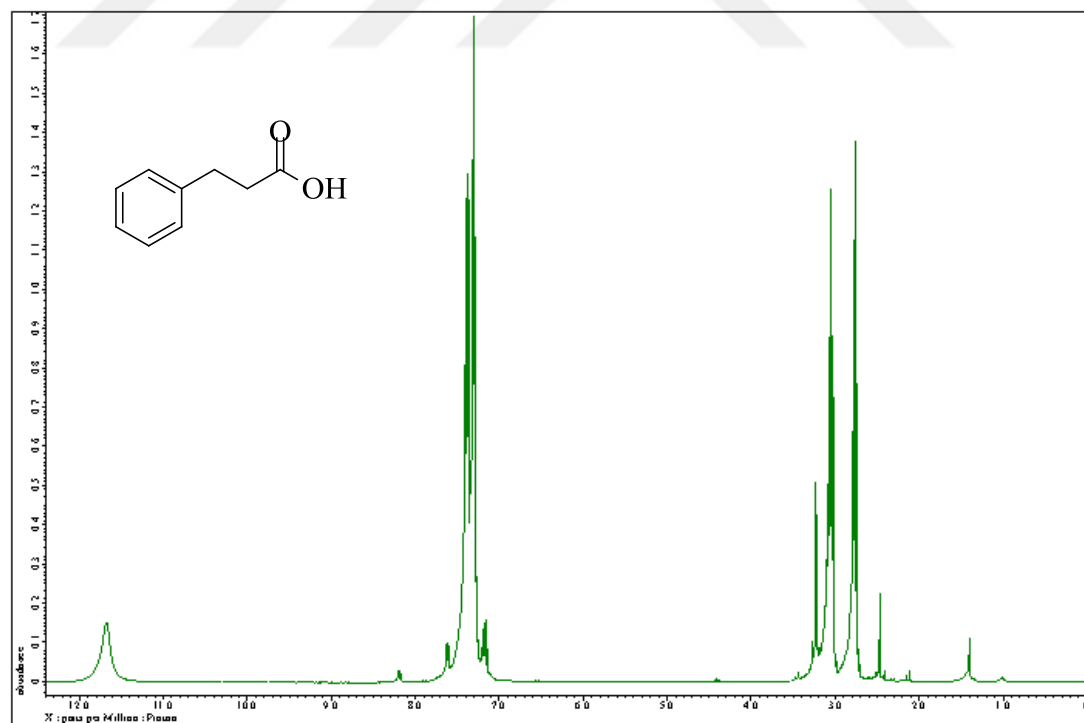


Figure A.130 ¹H NMR Spectrum of compound 211g

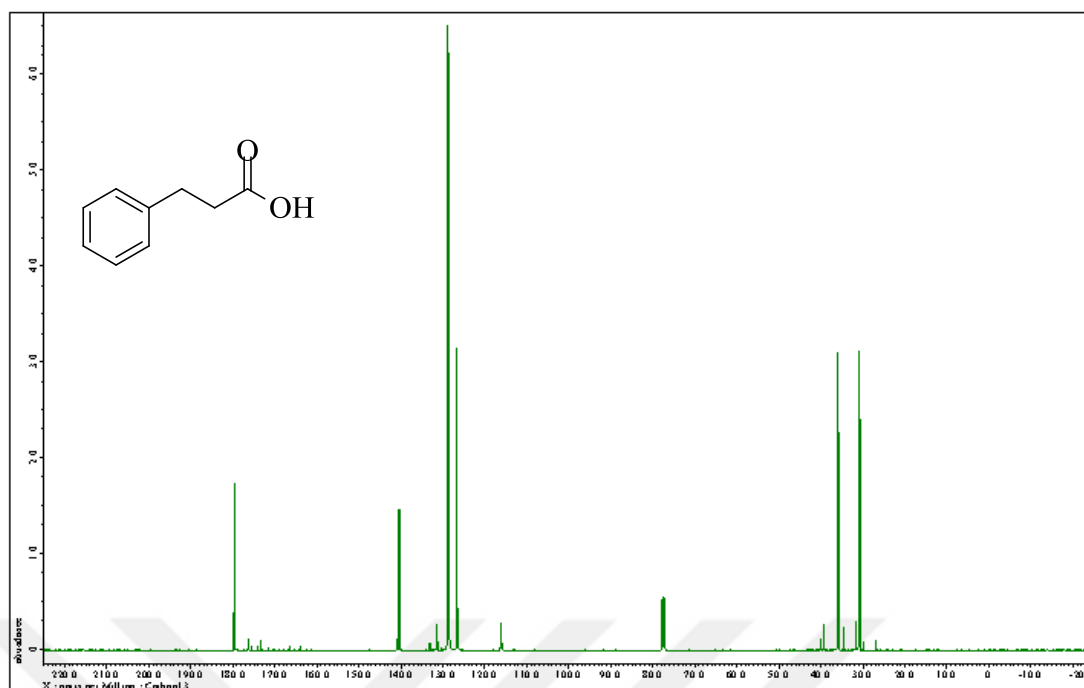


Figure A.131 ^{13}C NMR Spectrum of compound 211g

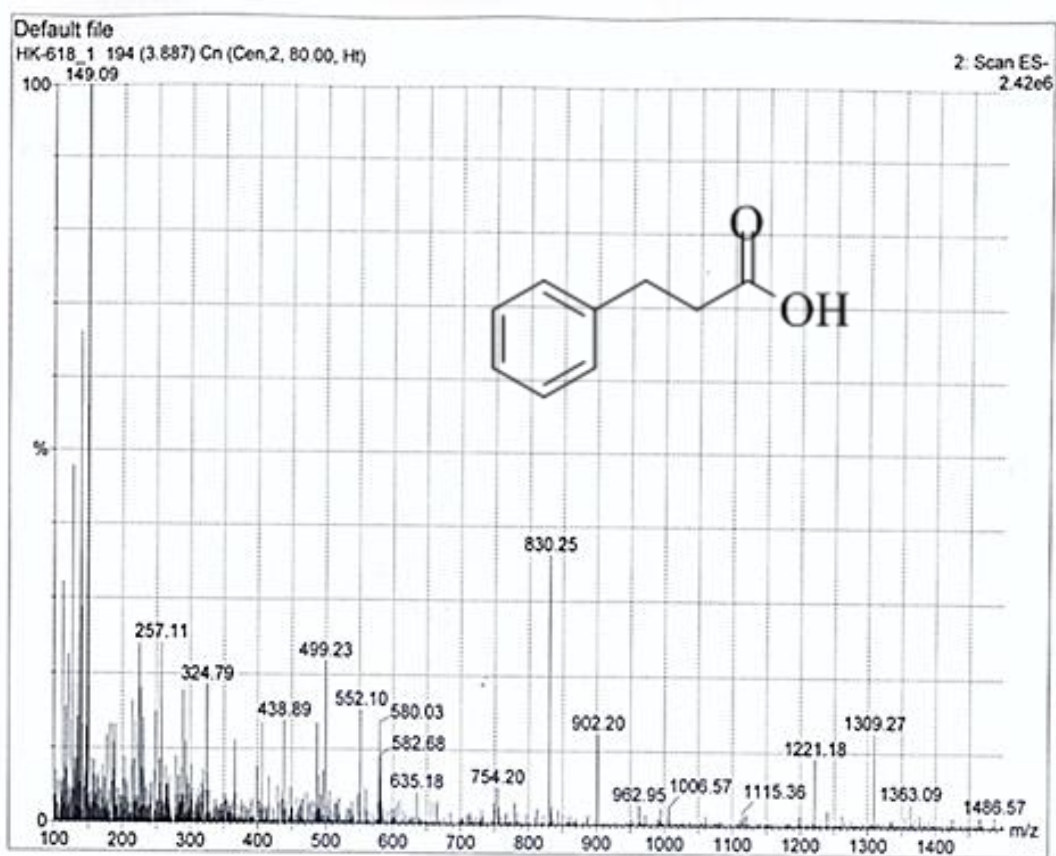


Figure A 132 MASS Spectrum of compound 211g

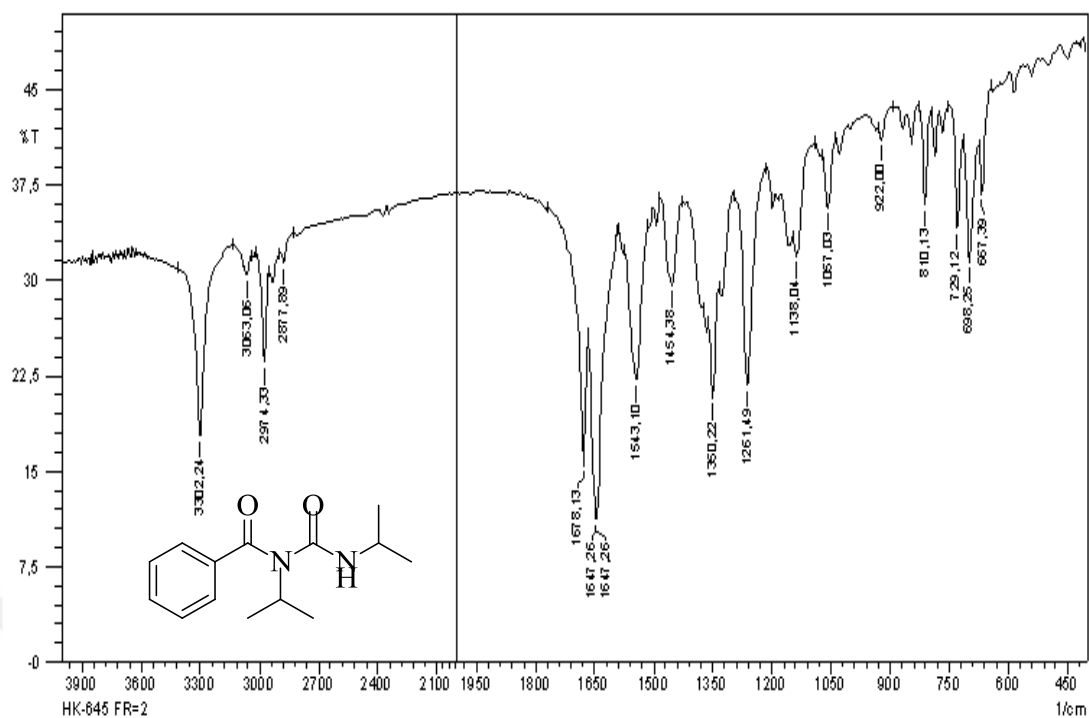


Figure A.133 IR Spectrum of compound **213a**

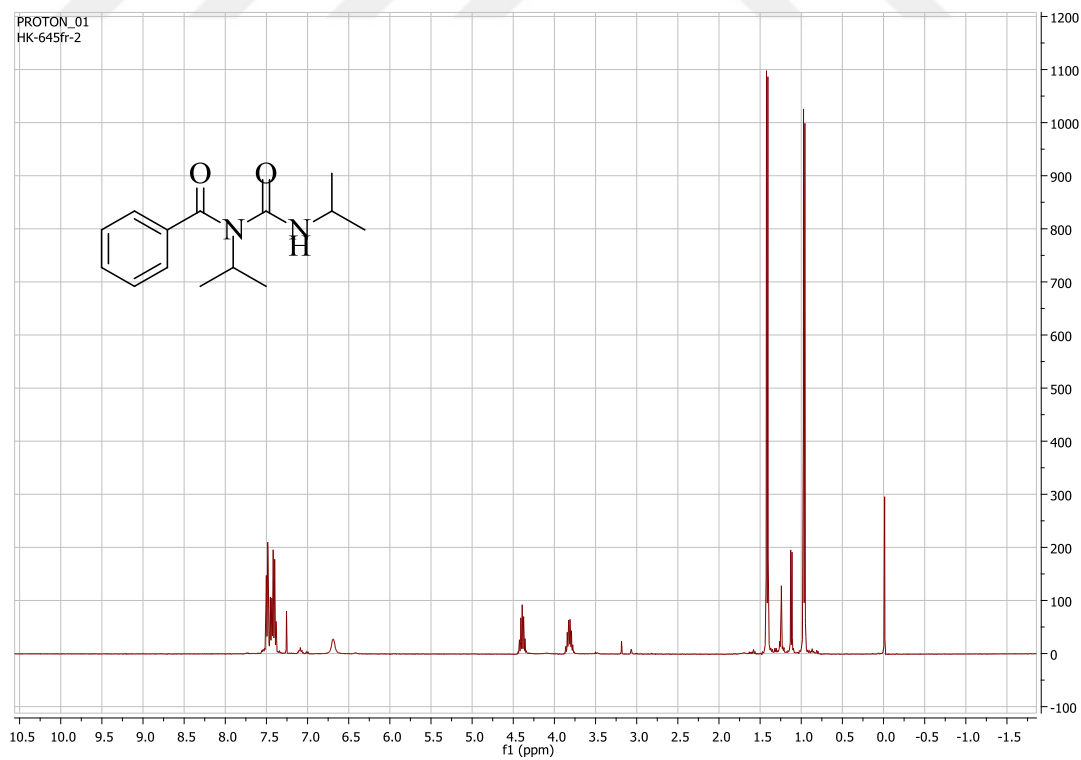
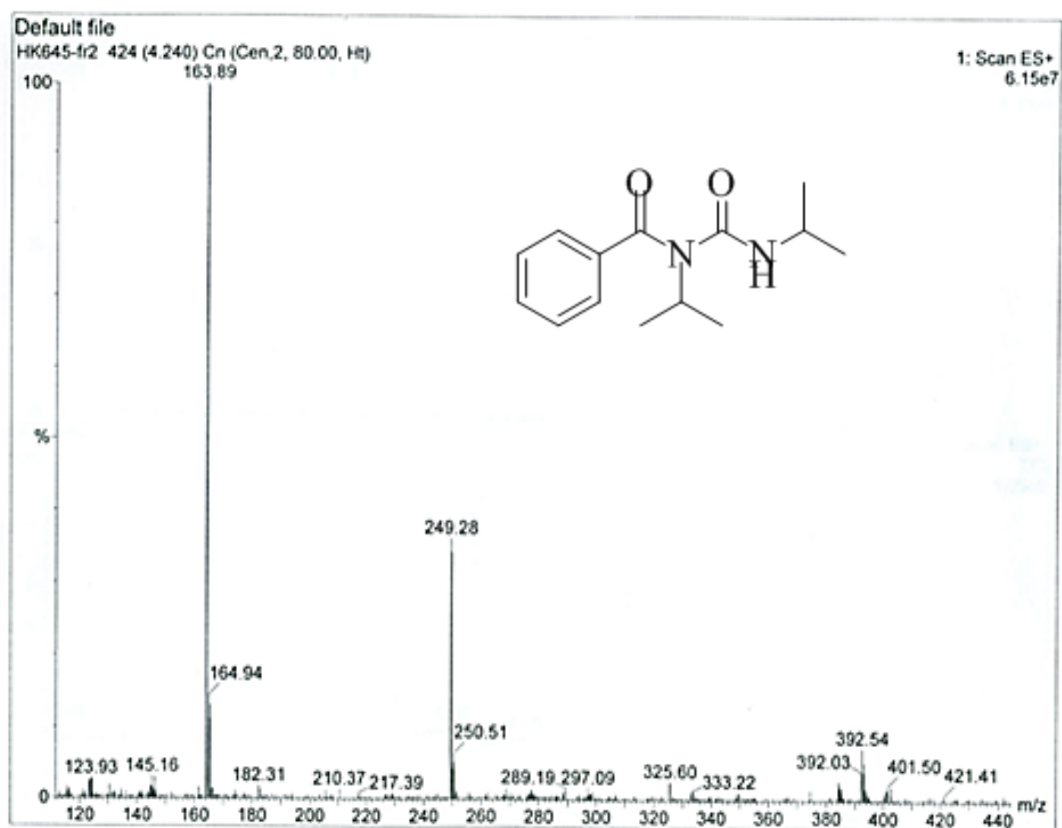
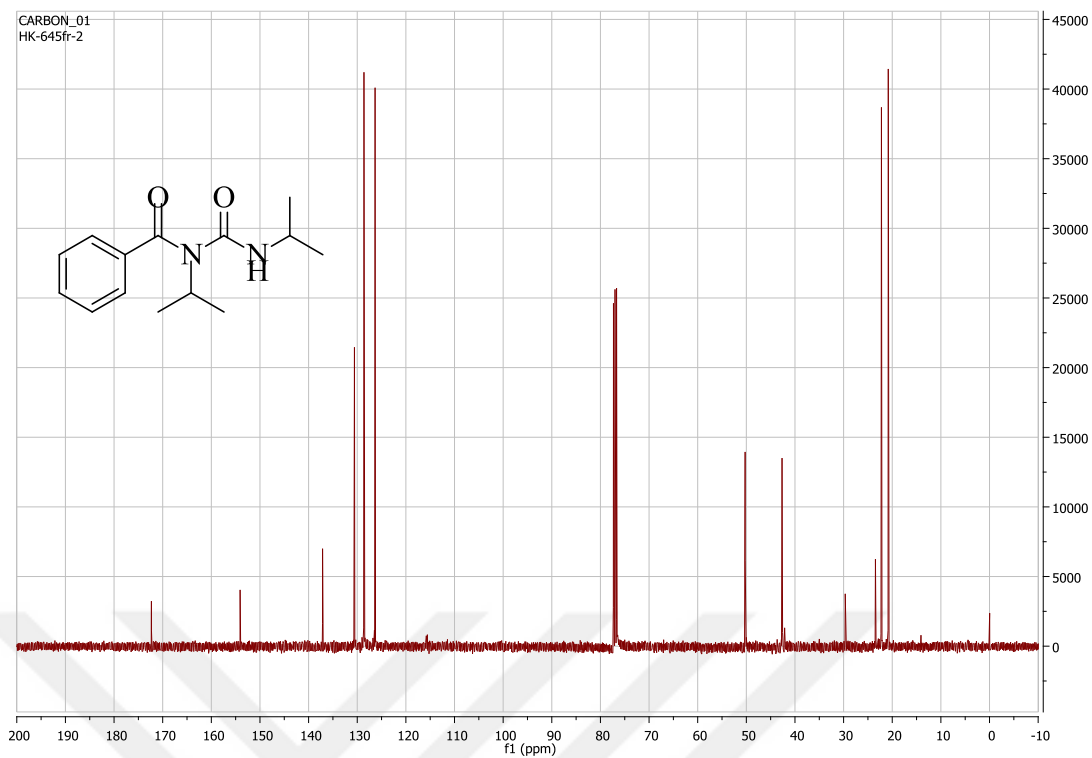


Figure A.134 ^1H NMR Spectrum of compound **213a**



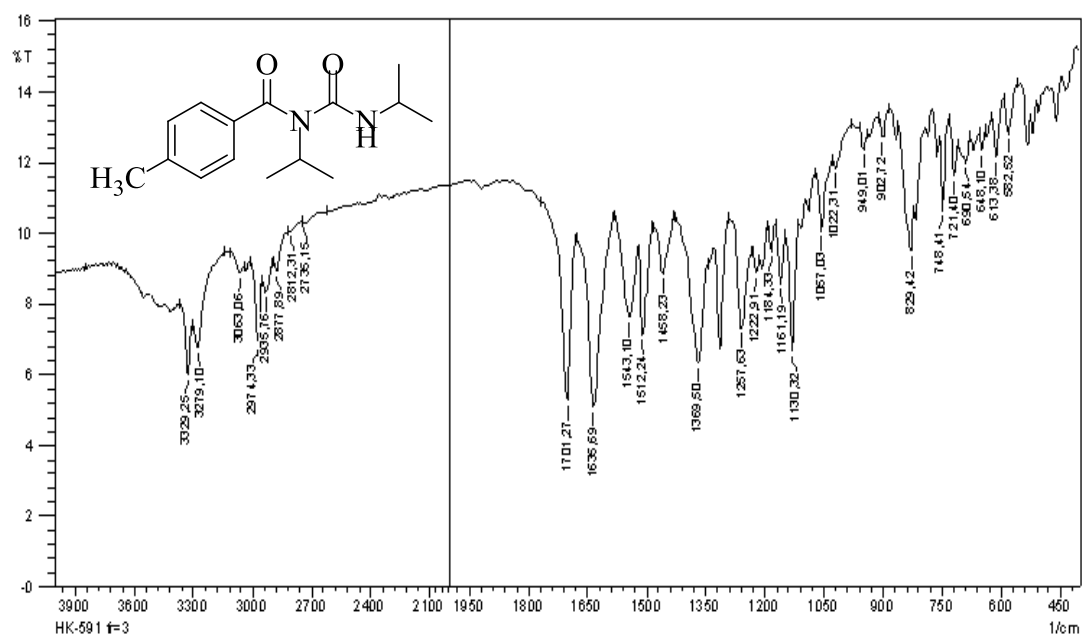


Figure A.137 IR Spectrum of compound **213b**

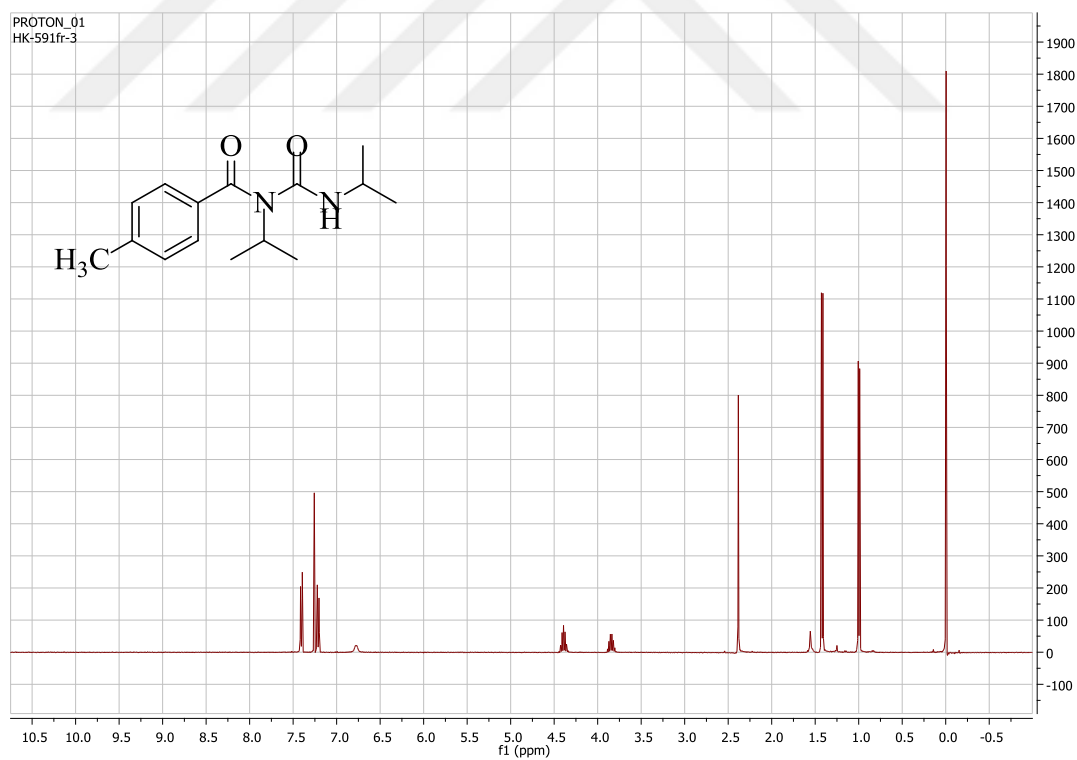


Figure A.138 ^1H NMR Spectrum of compound **213b**

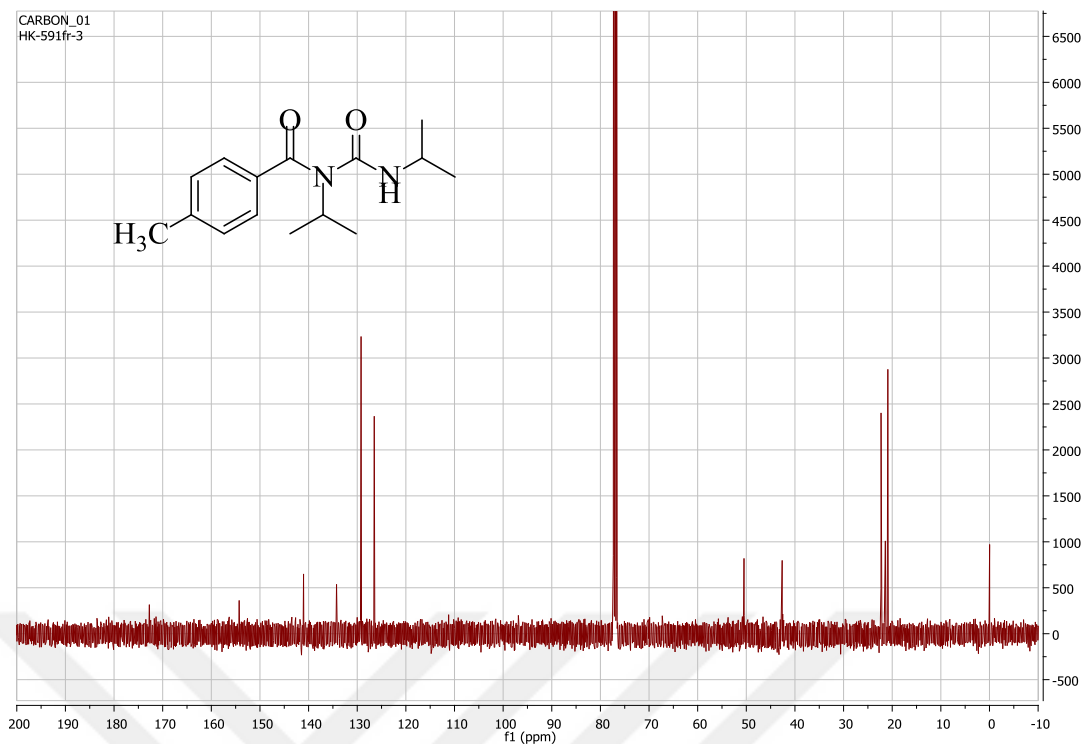


Figure A.139 ¹³C NMR Spectrum of compound 213b

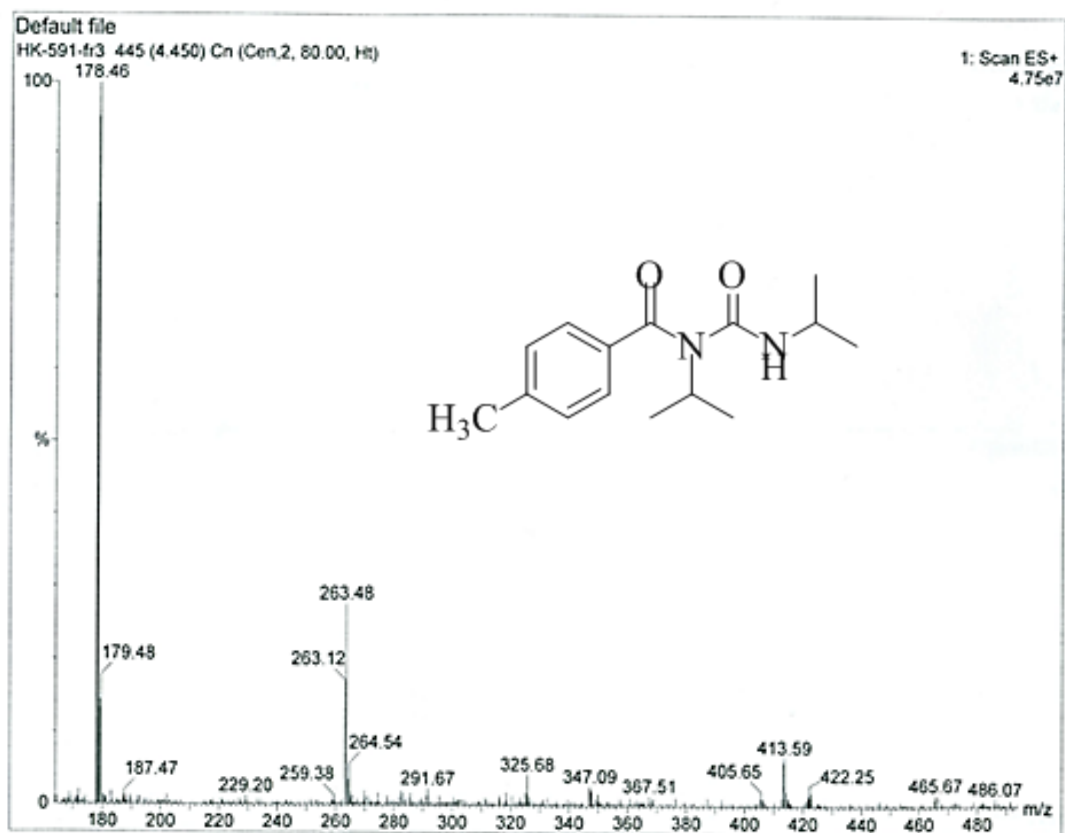


Figure A.140 MASS Spectrum of compound 213b

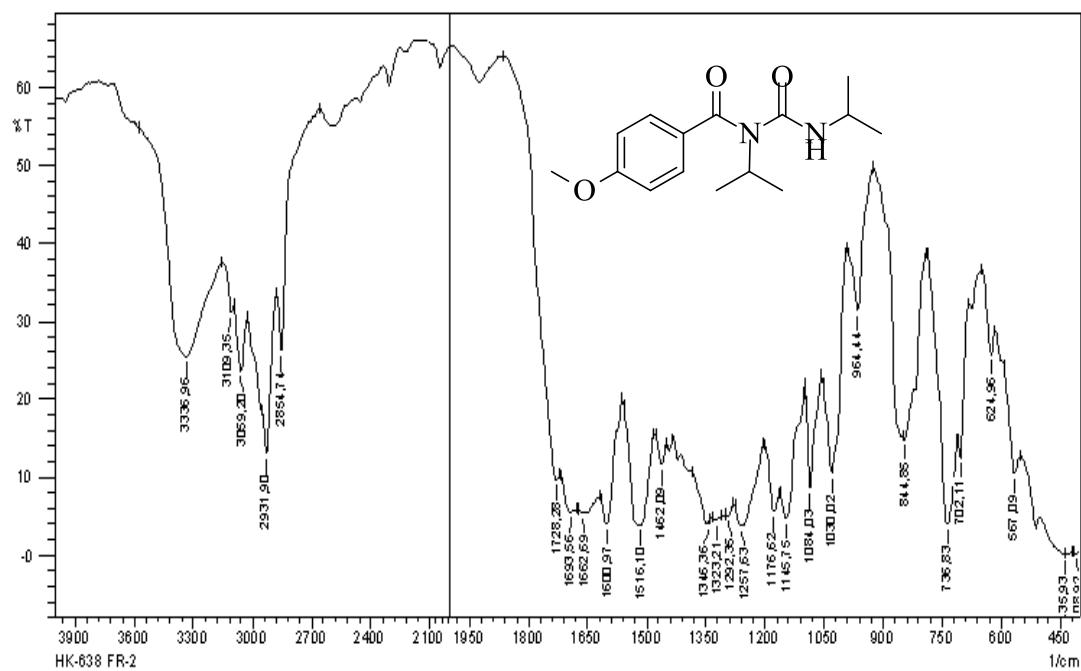


Figure A.141 IR Spectrum of compound **213c**

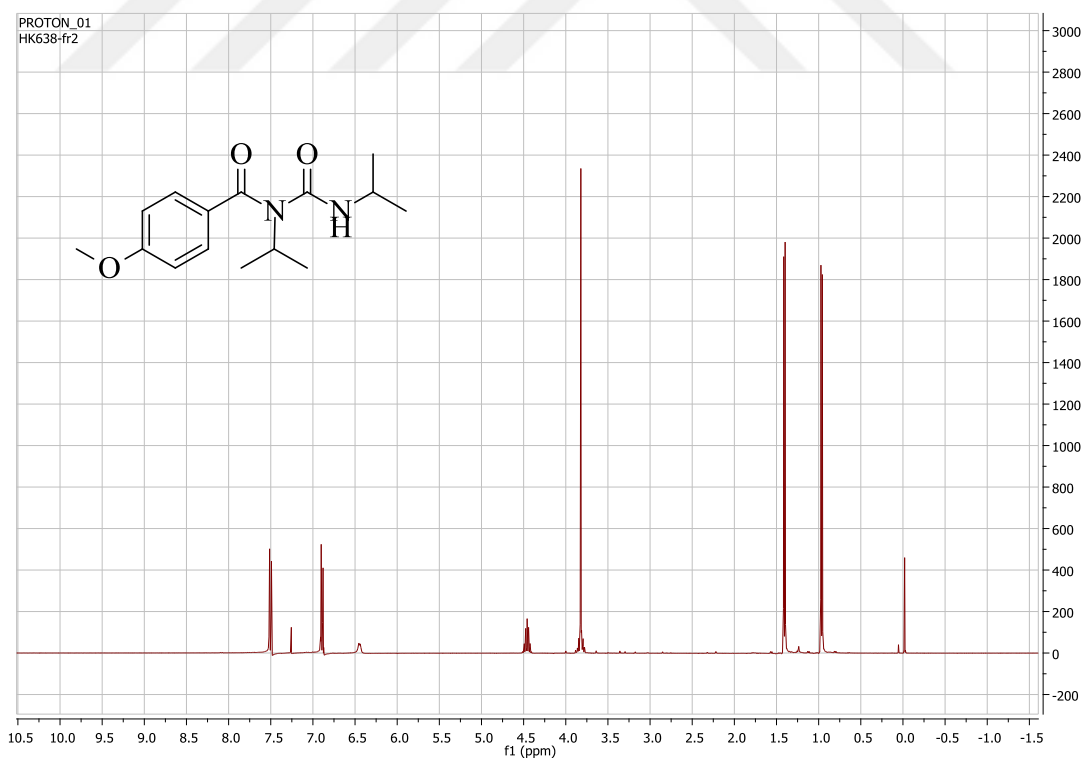


Figure A.142 ¹H NMR Spectrum of compound **213c**

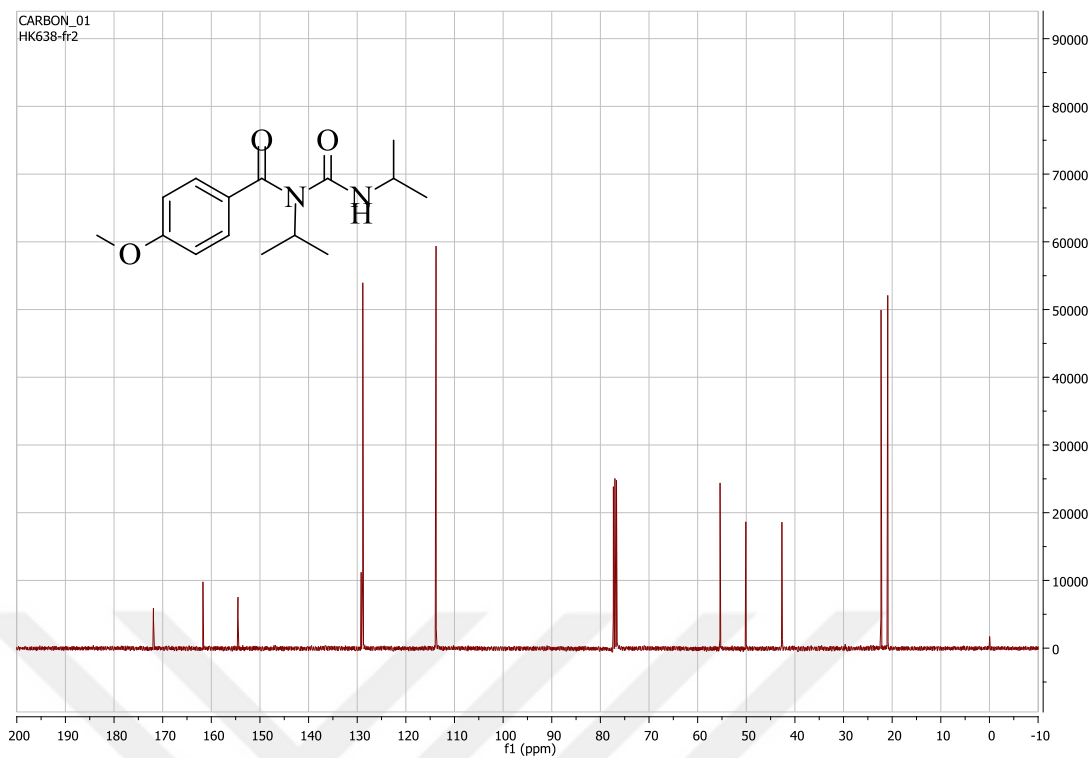


Figure A.143 ^{13}C NMR Spectrum of compound **213c**

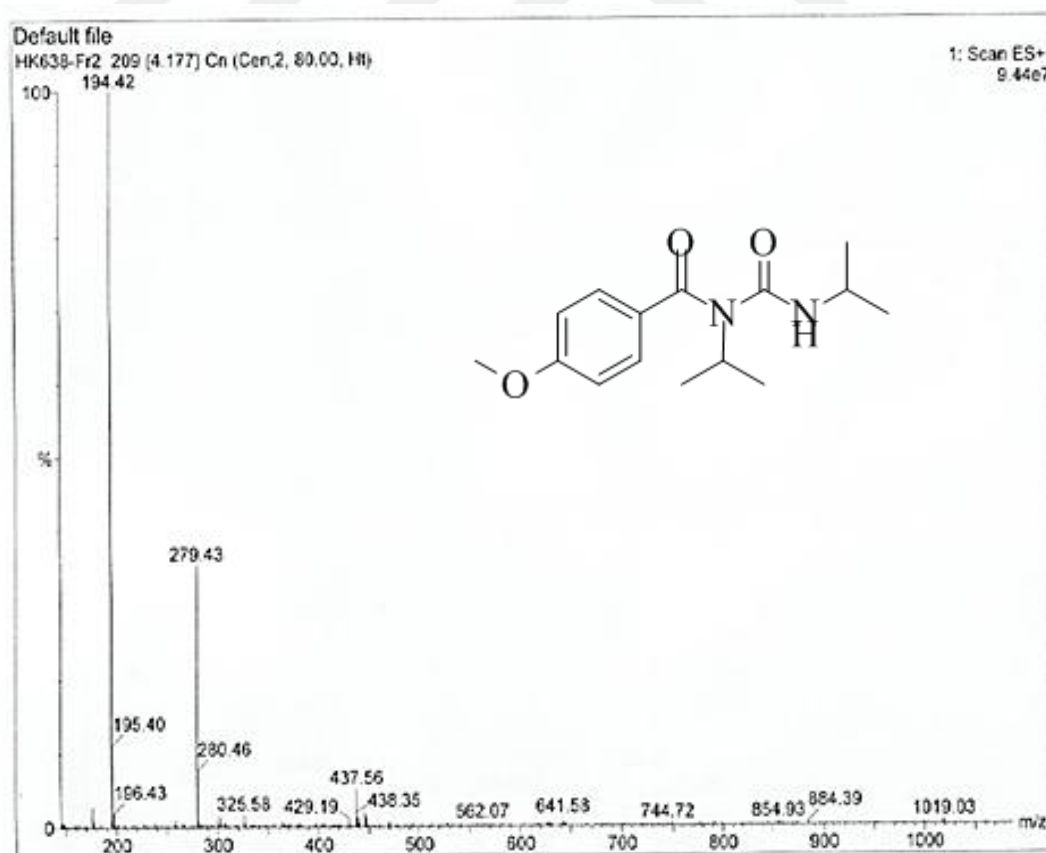


Figure A.144 MASS Spectrum of compound **213c**

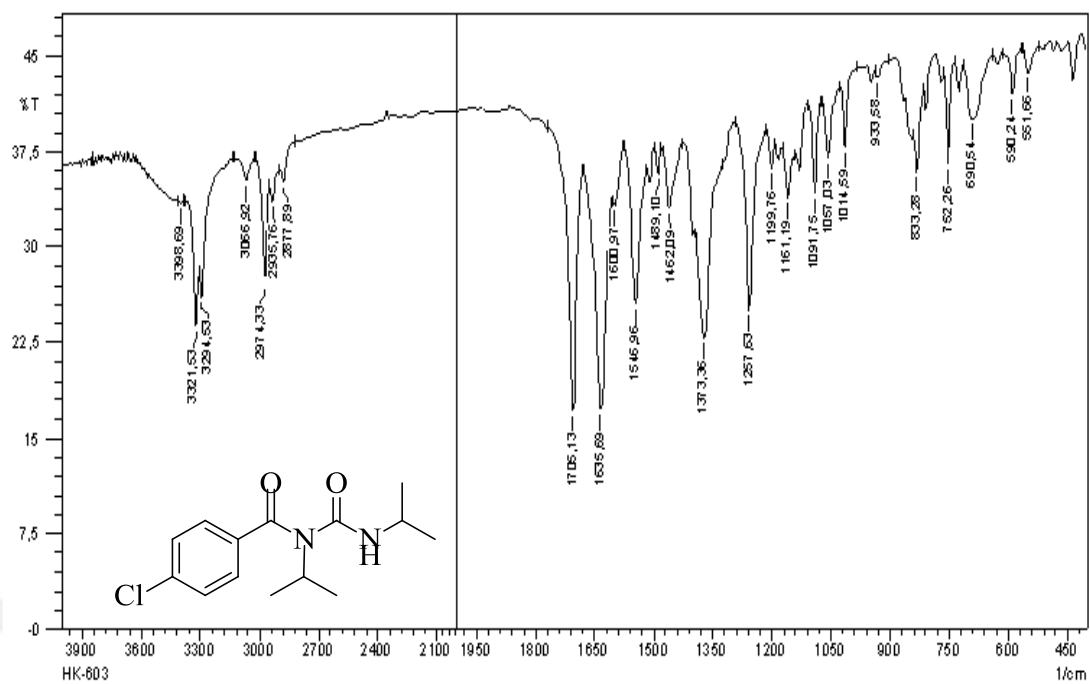


Figure A.145 IR Spectrum of compound **213d**

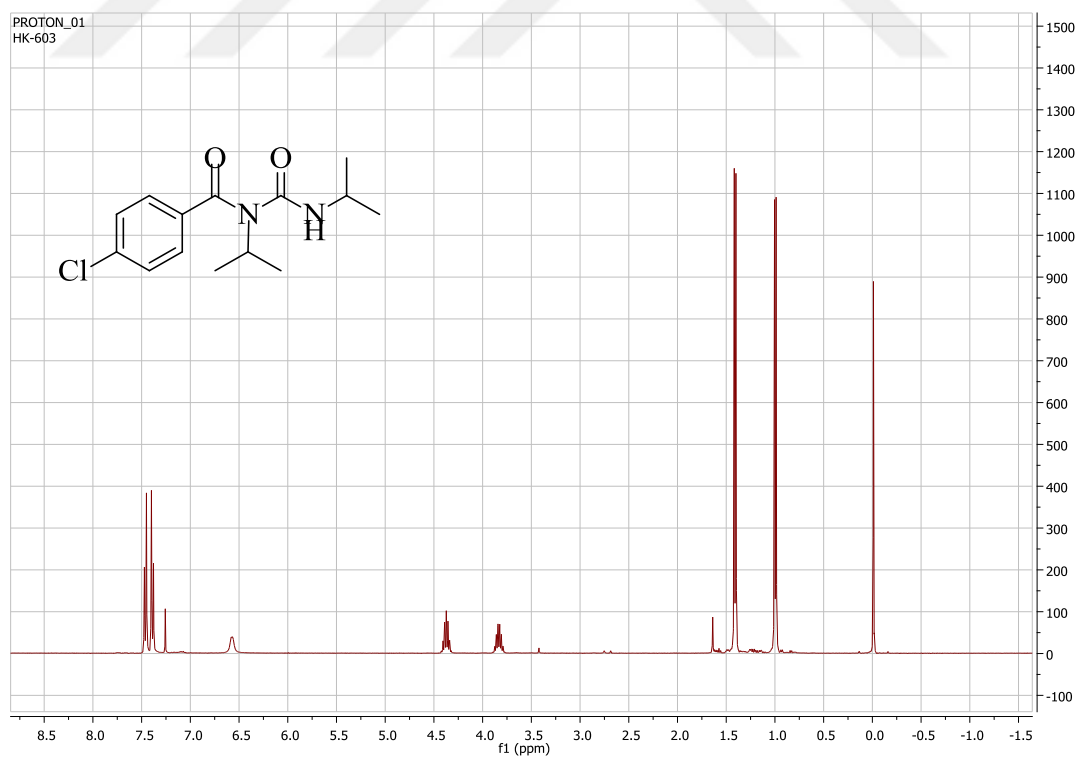


Figure A.146 ¹H NMR Spectrum of compound **213d**

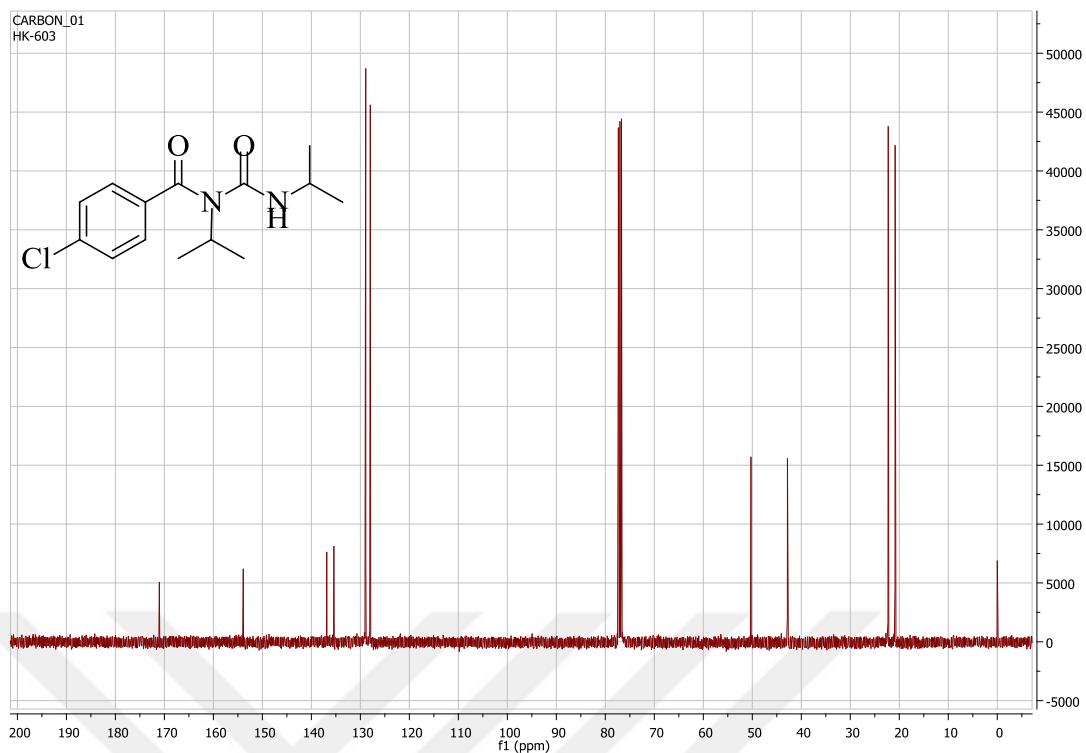


Figure A.147 ¹³C NMR Spectrum of compound 213d

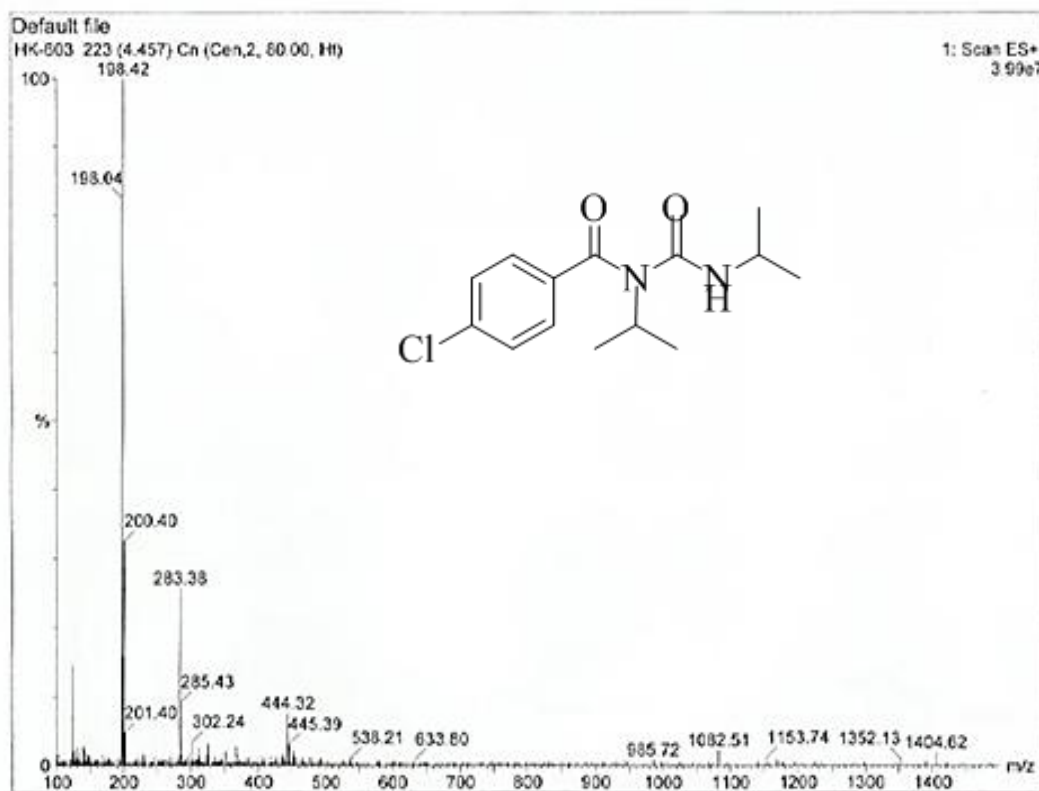


Figure A.148 MASS Spectrum of compound 213d

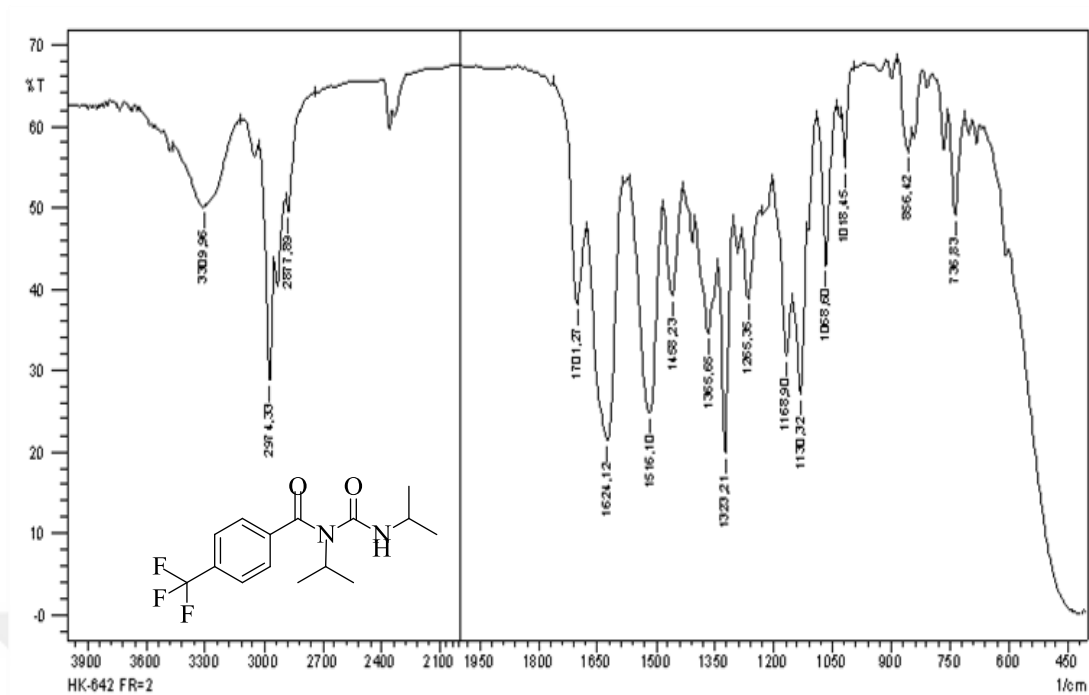


Figure A.149 IR Spectrum of compound **213e**

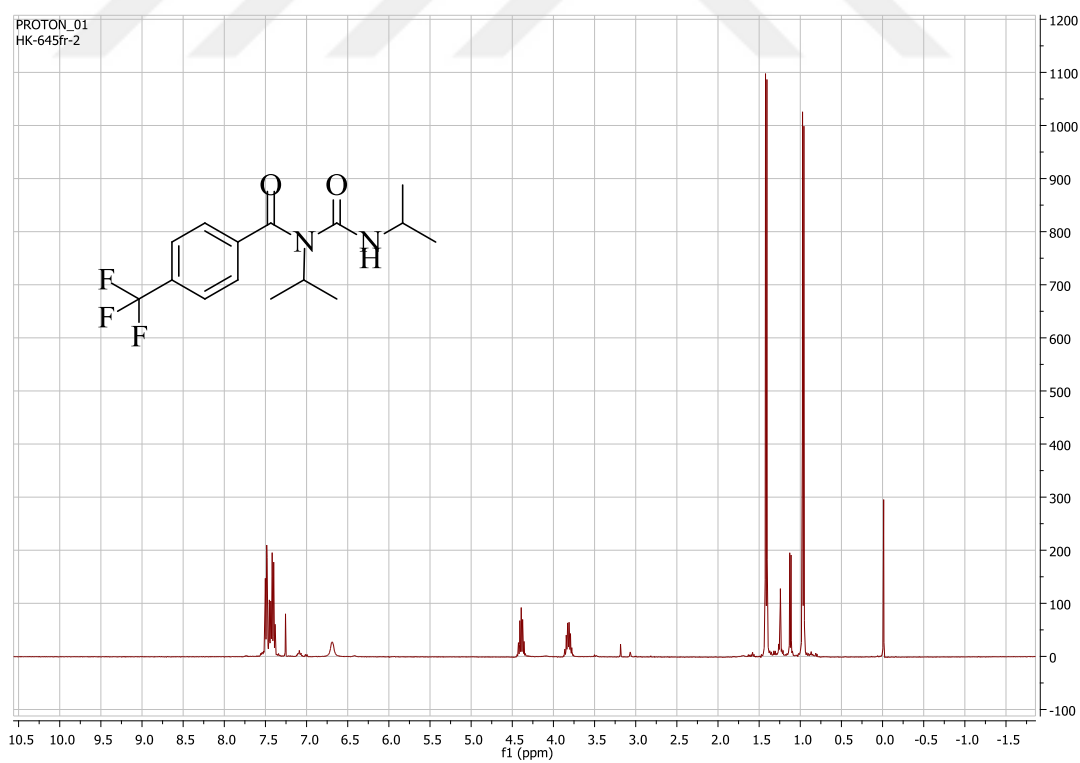


Figure A.150 ^1H NMR Spectrum of compound **213e**

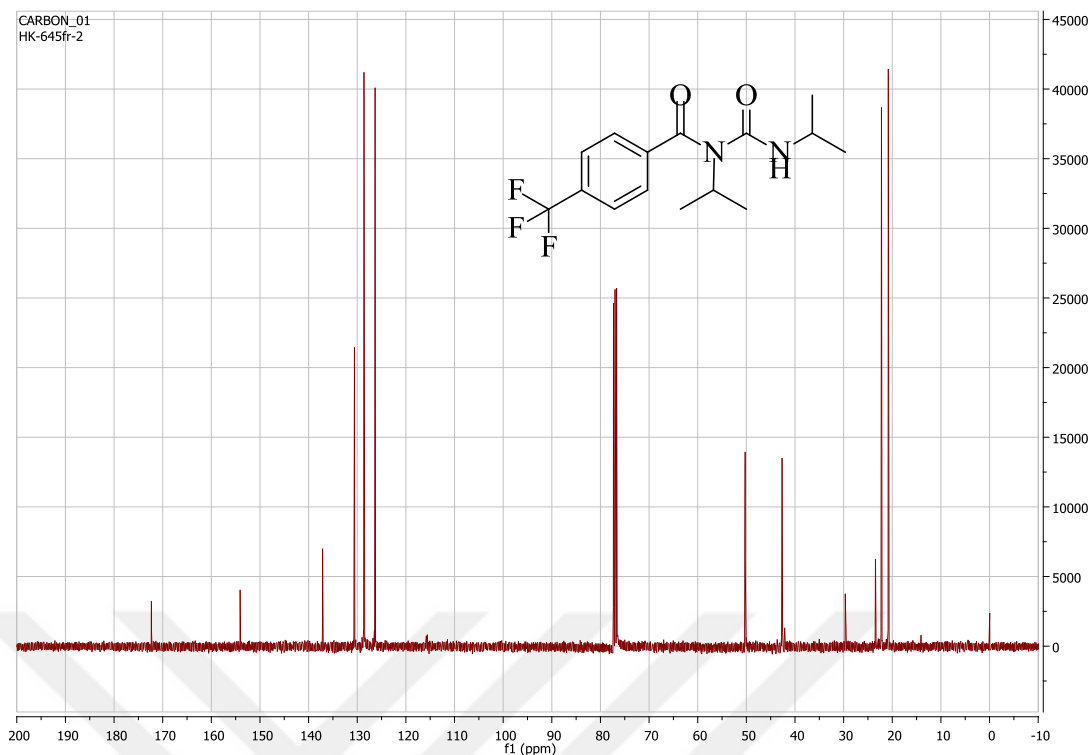


Figure A.151 ¹³C NMR Spectrum of compound 213e

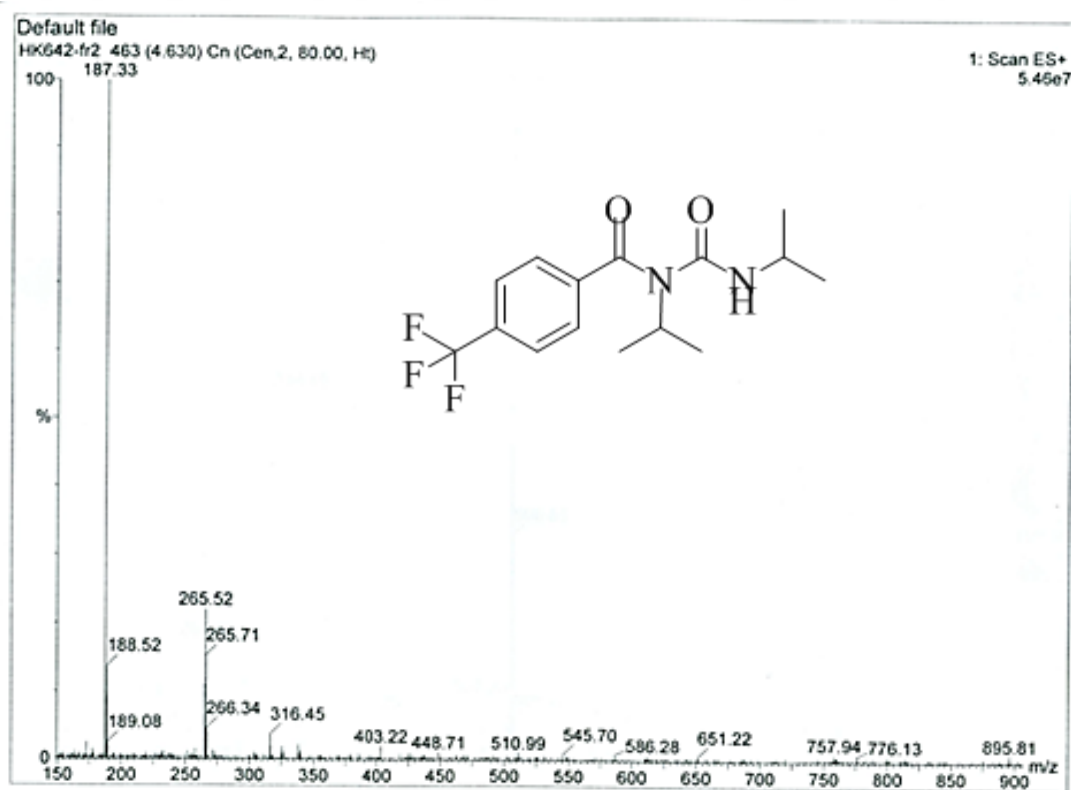


Figure A.152 MASS Spectrum of compound 213e

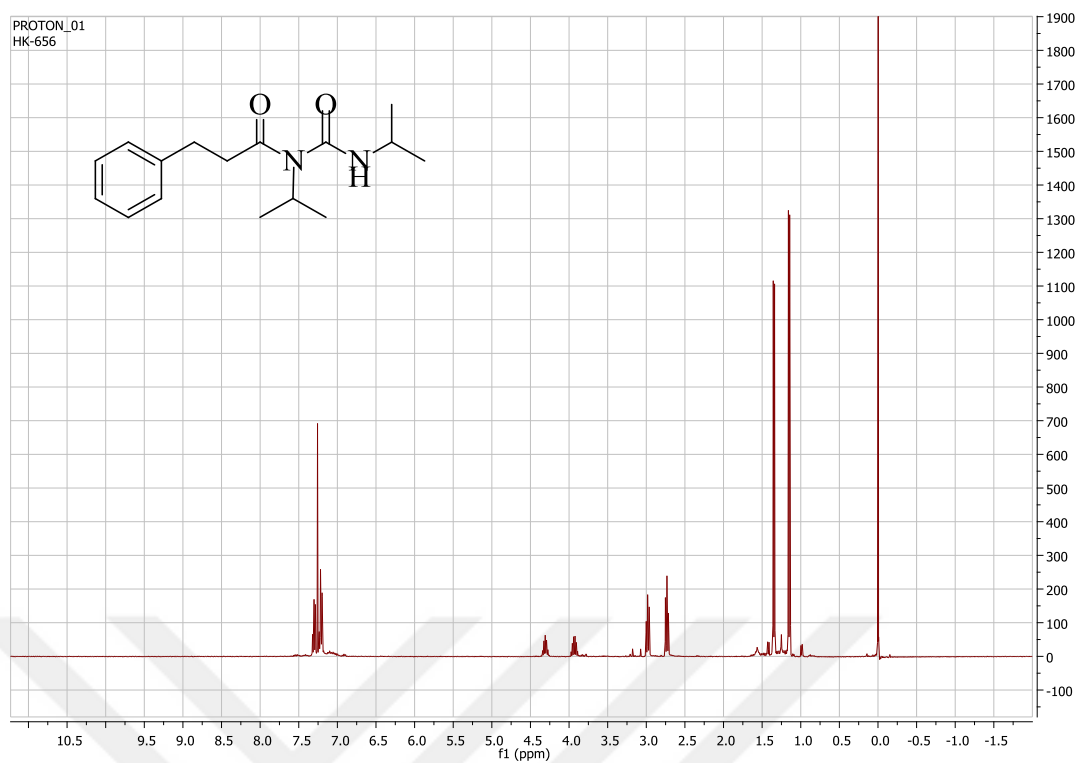


Figure A.153 ¹H NMR Spectrum of compound **213f**

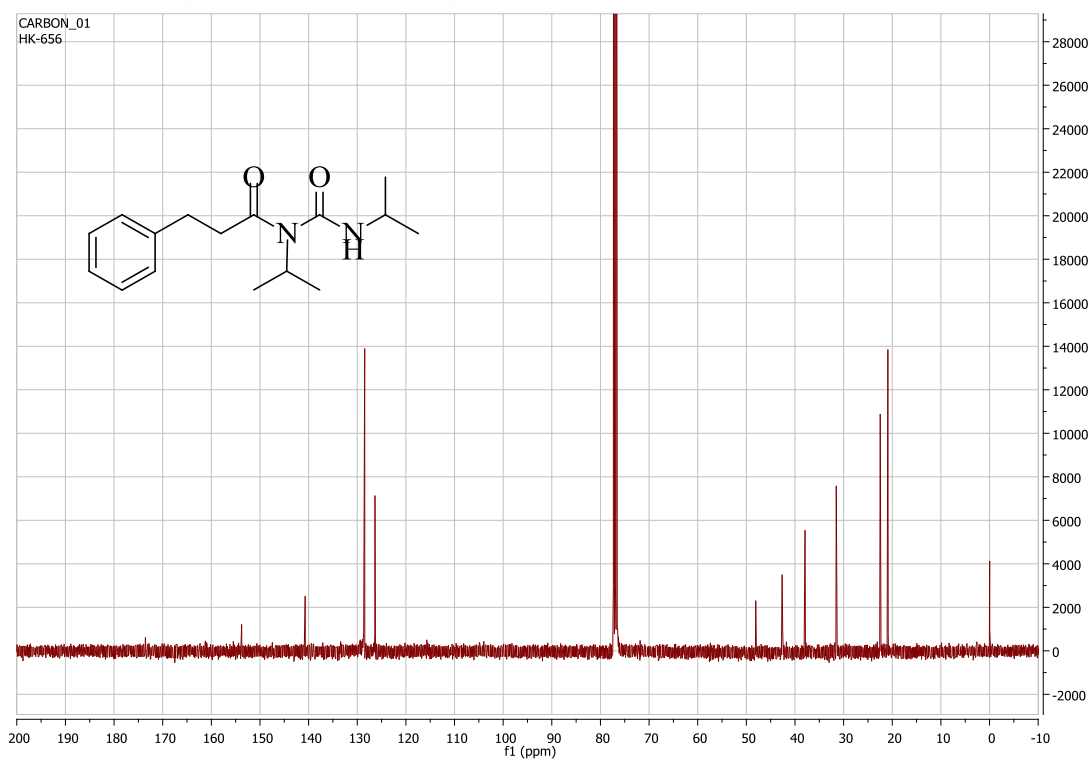


Figure A.154 ¹³C NMR Spectrum of compound **213f**

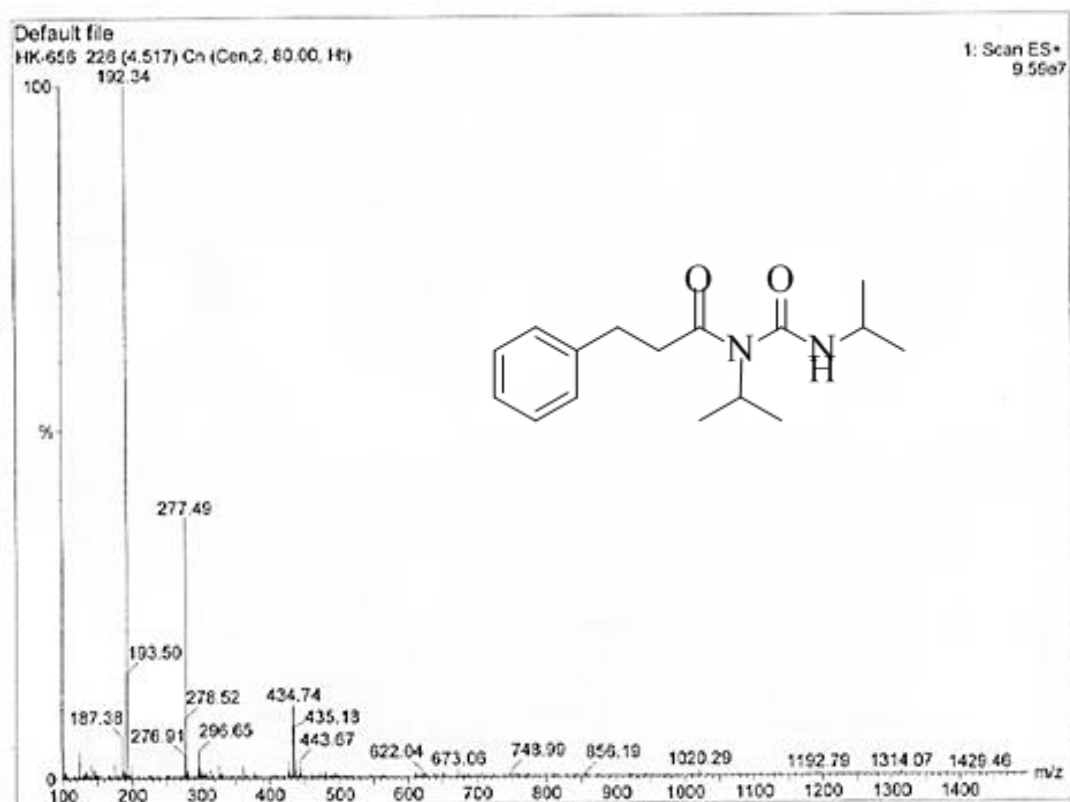


Figure A.155 MASS Spectrum of compound 213f

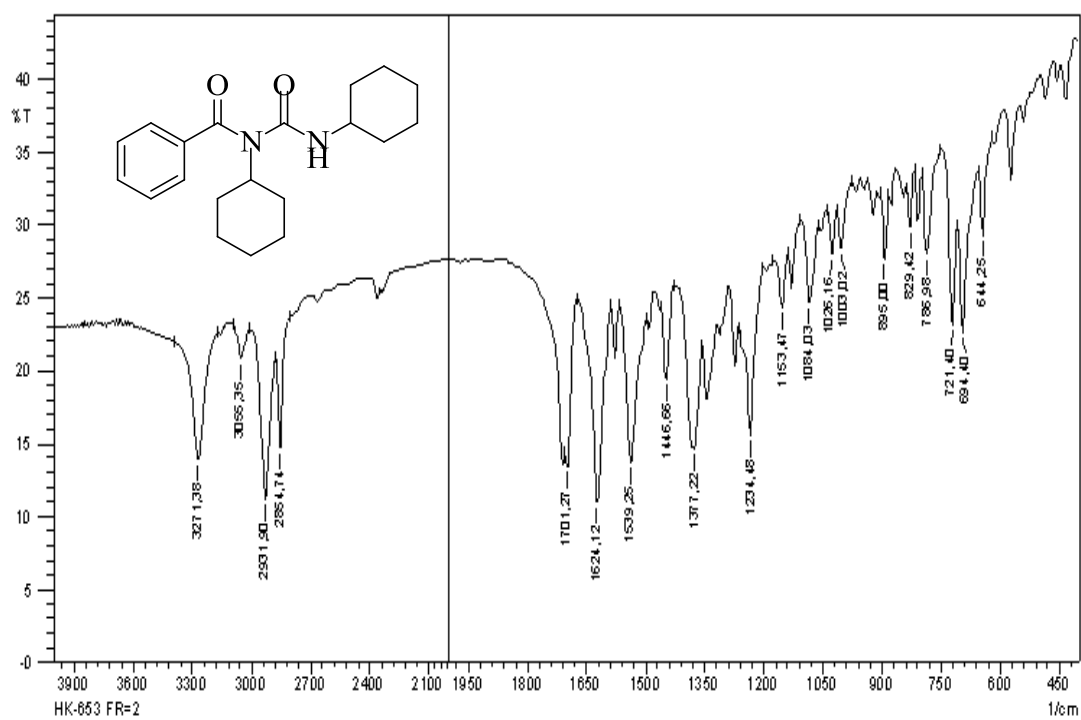


Figure A.156 IR Spectrum of compound 214a

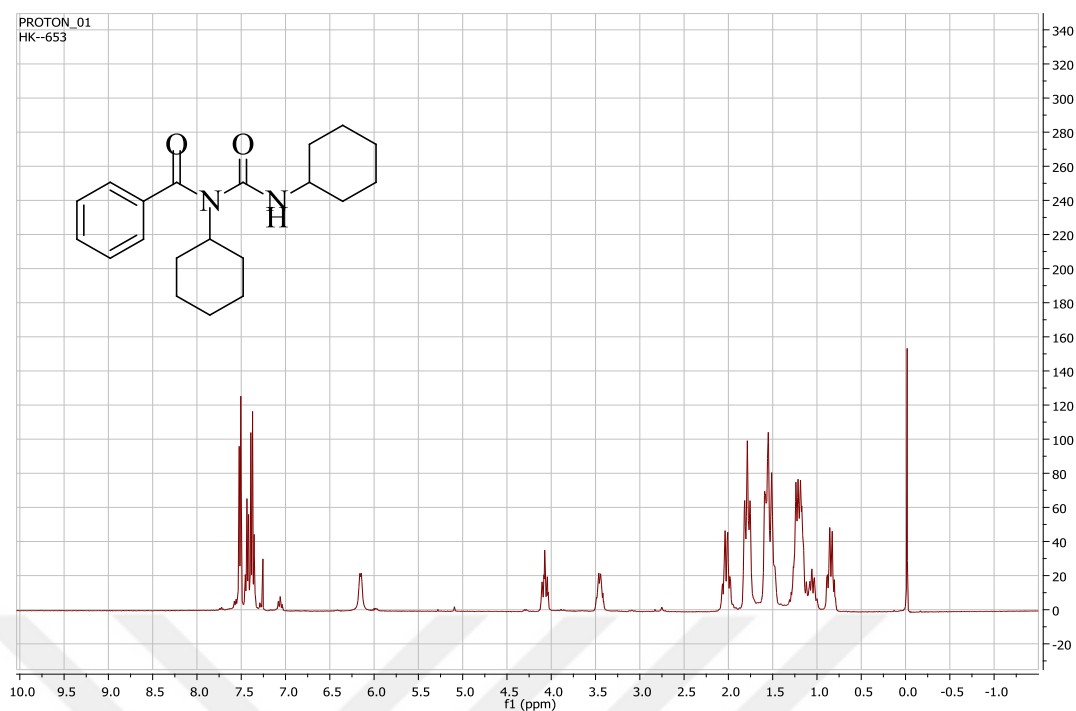


Figure A.157 ¹H NMR Spectrum of compound 214a

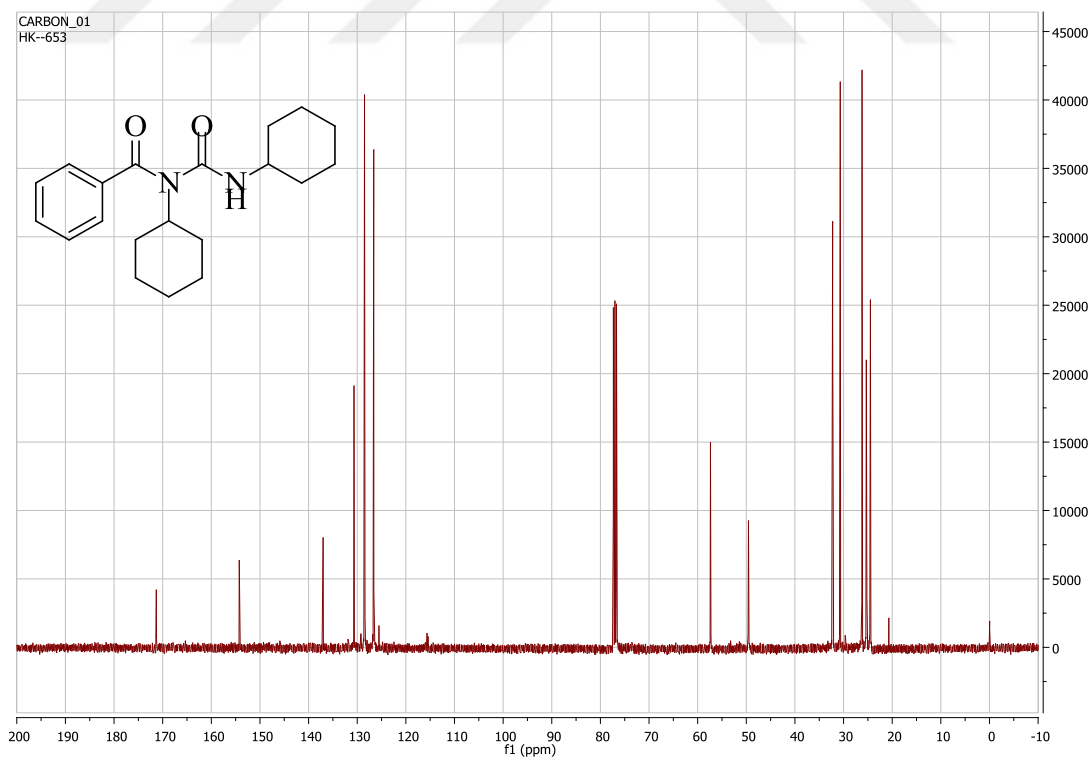


Figure A.158 ¹³C NMR Spectrum of compound 214a

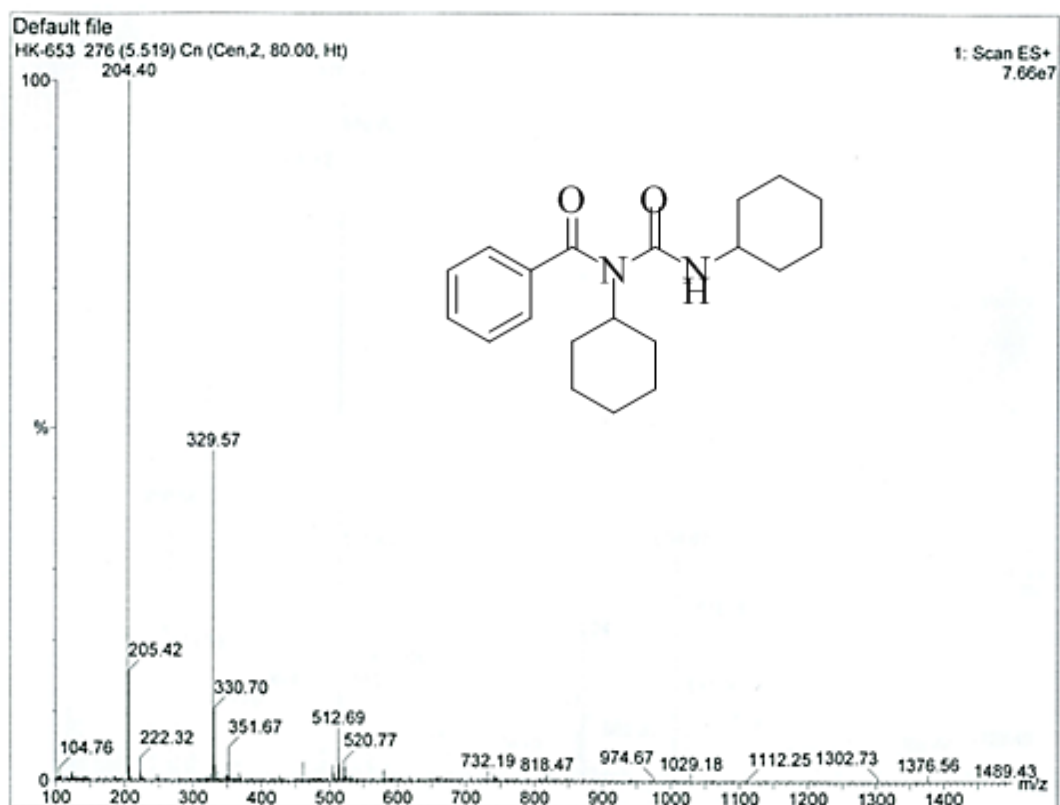


Figure A.159 MASS Spectrum of compound 214a

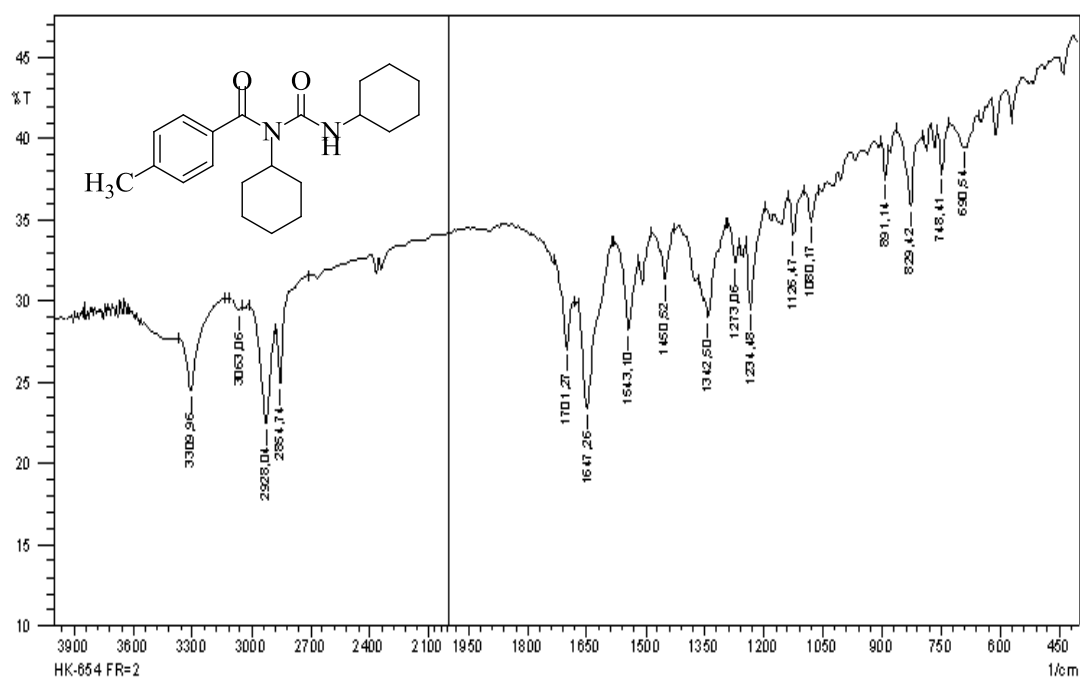


Figure A.160 IR Spectrum of compound 214b

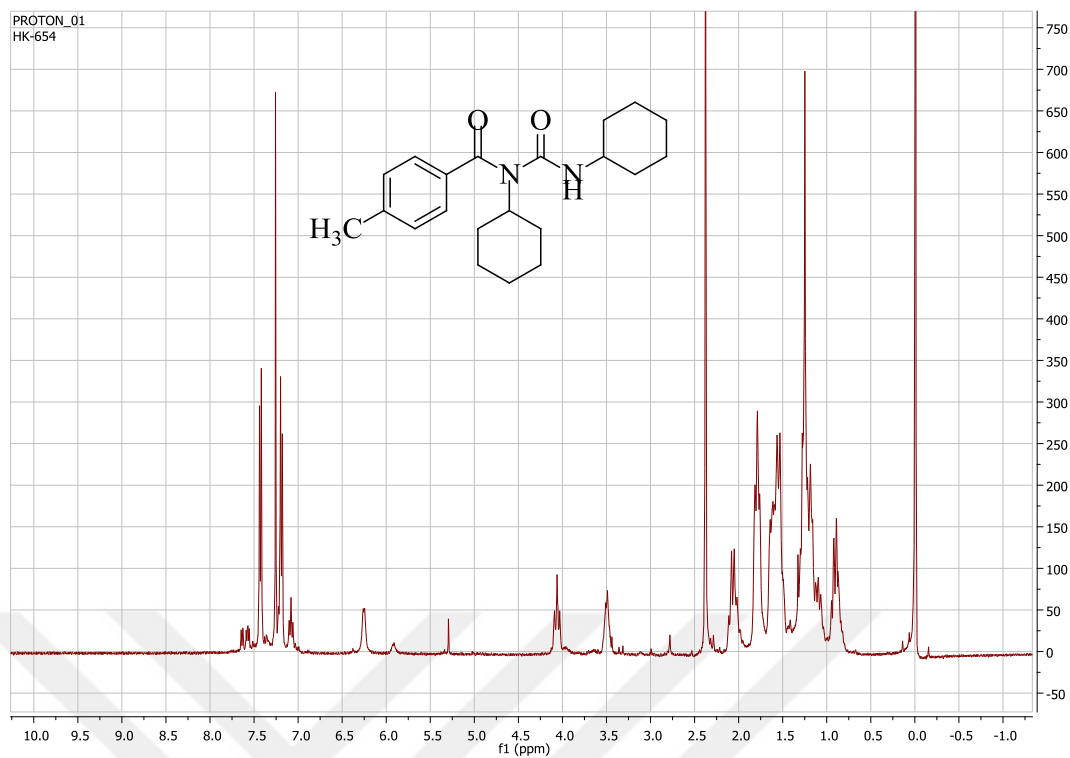


Figure A.161 ¹H NMR Spectrum of compound 214b

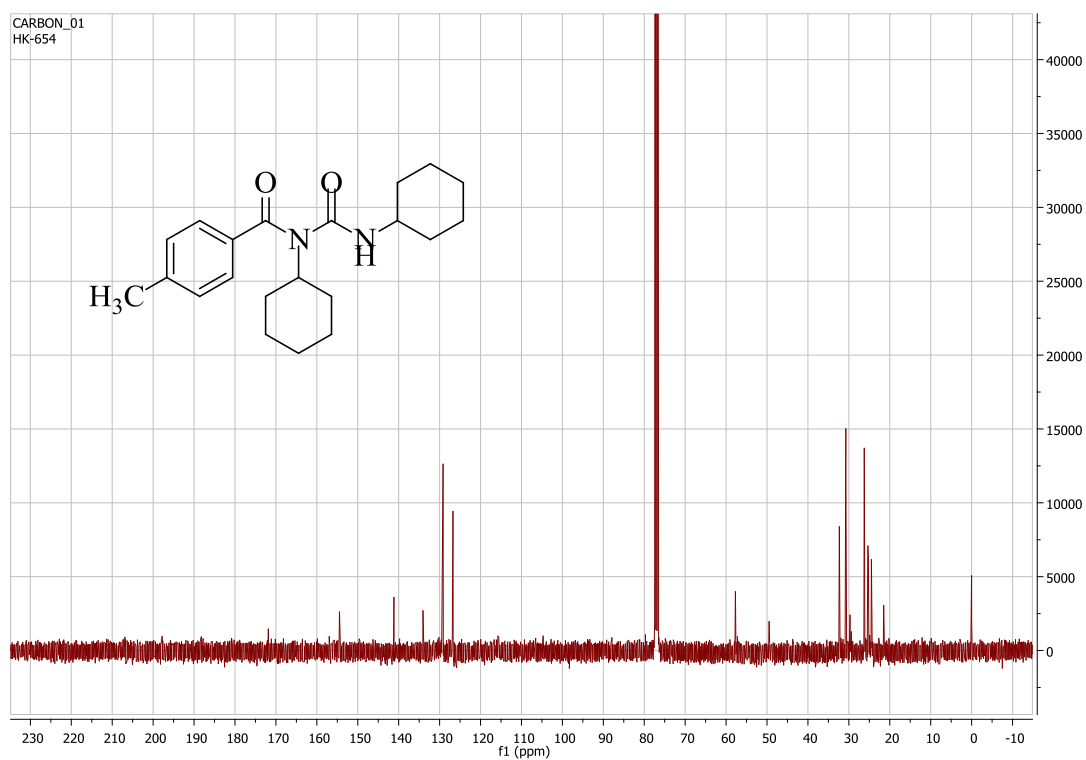


Figure A.162 ¹³C NMR Spectrum of compound 214b

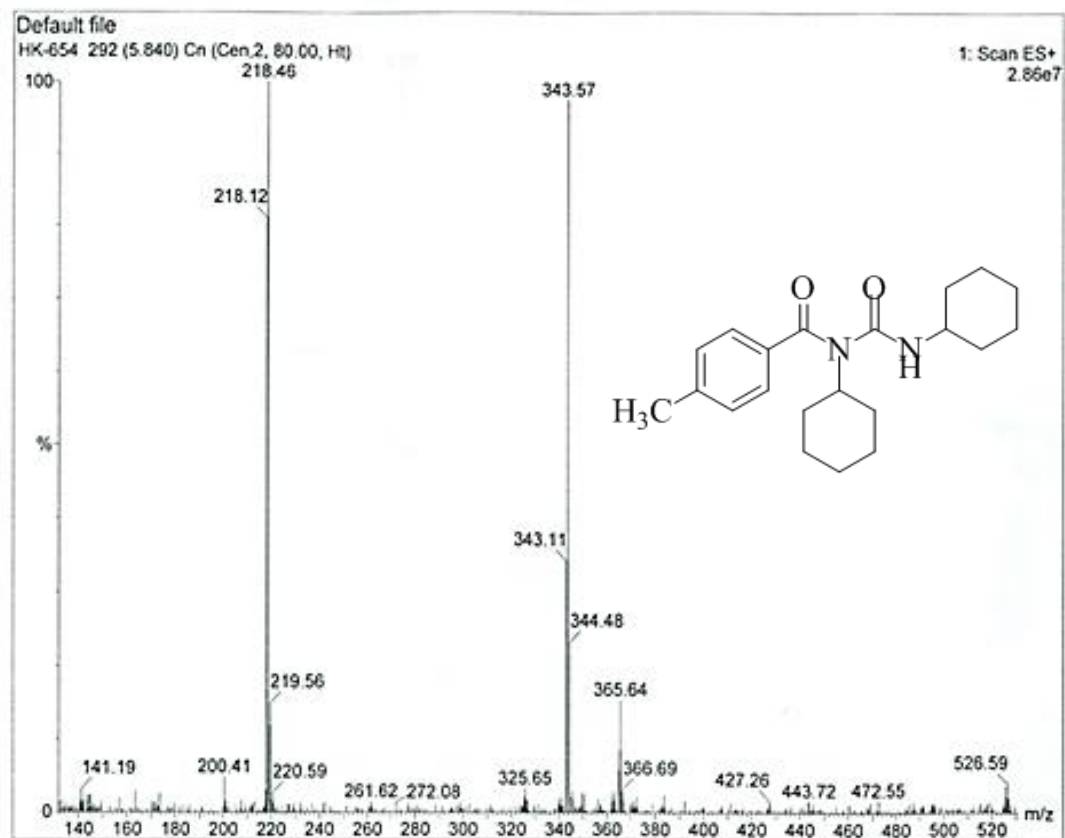


Figure A.163 MASS Spectrum of compound 214b

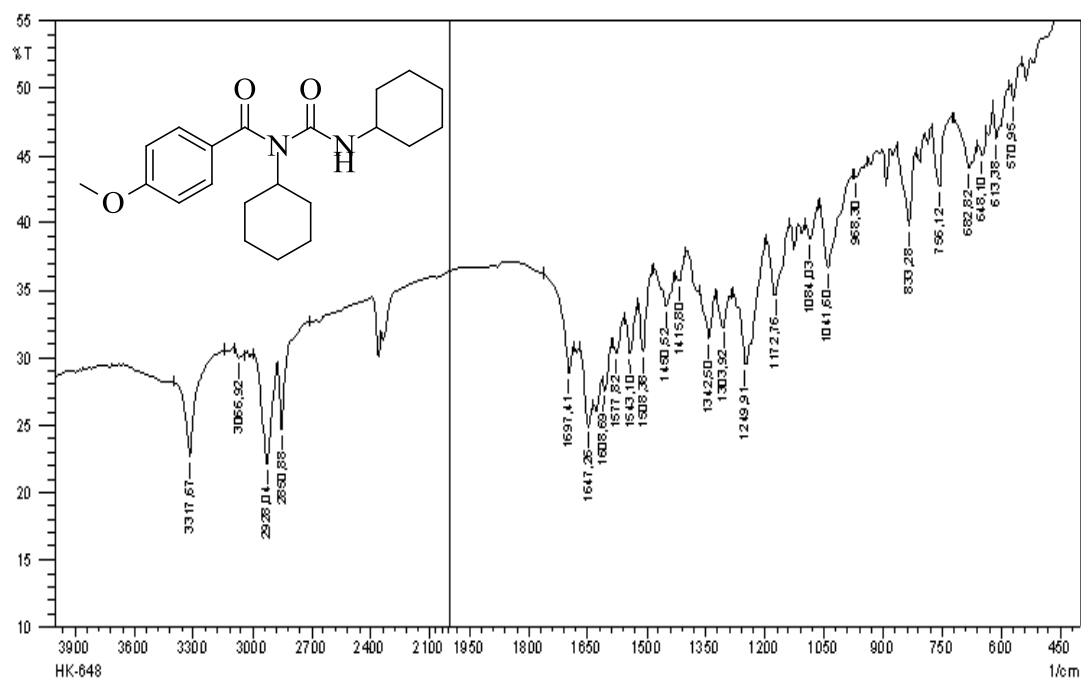


Figure A.164 IR Spectrum of compound 214c

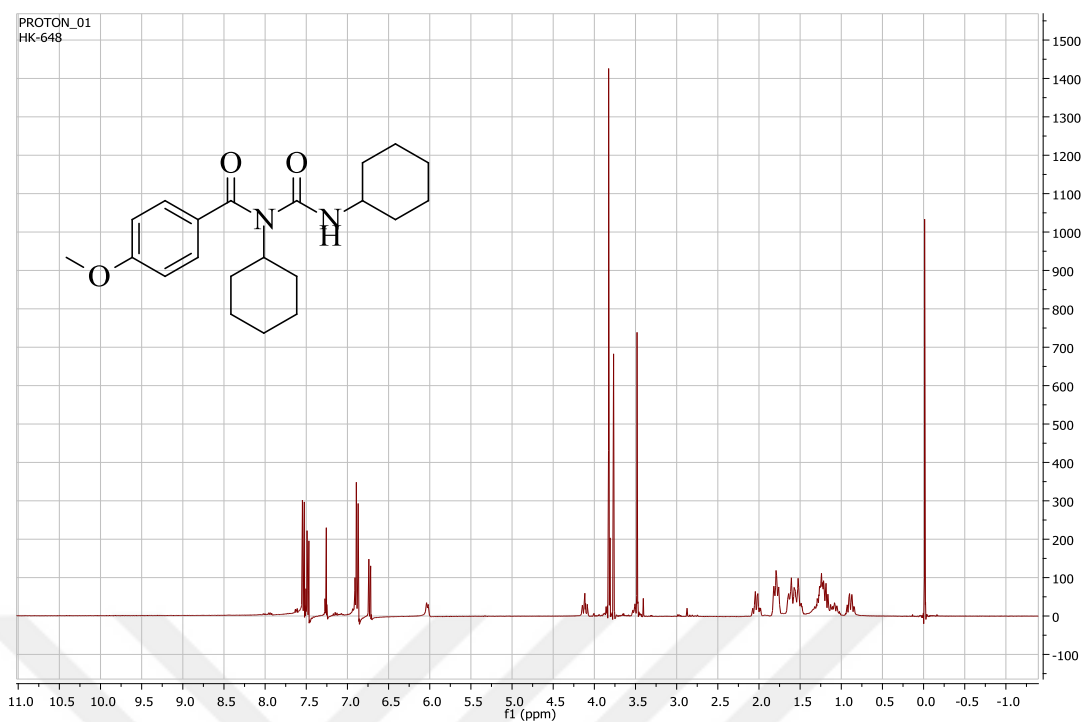


Figure A.165 ¹H NMR Spectrum of compound 214c

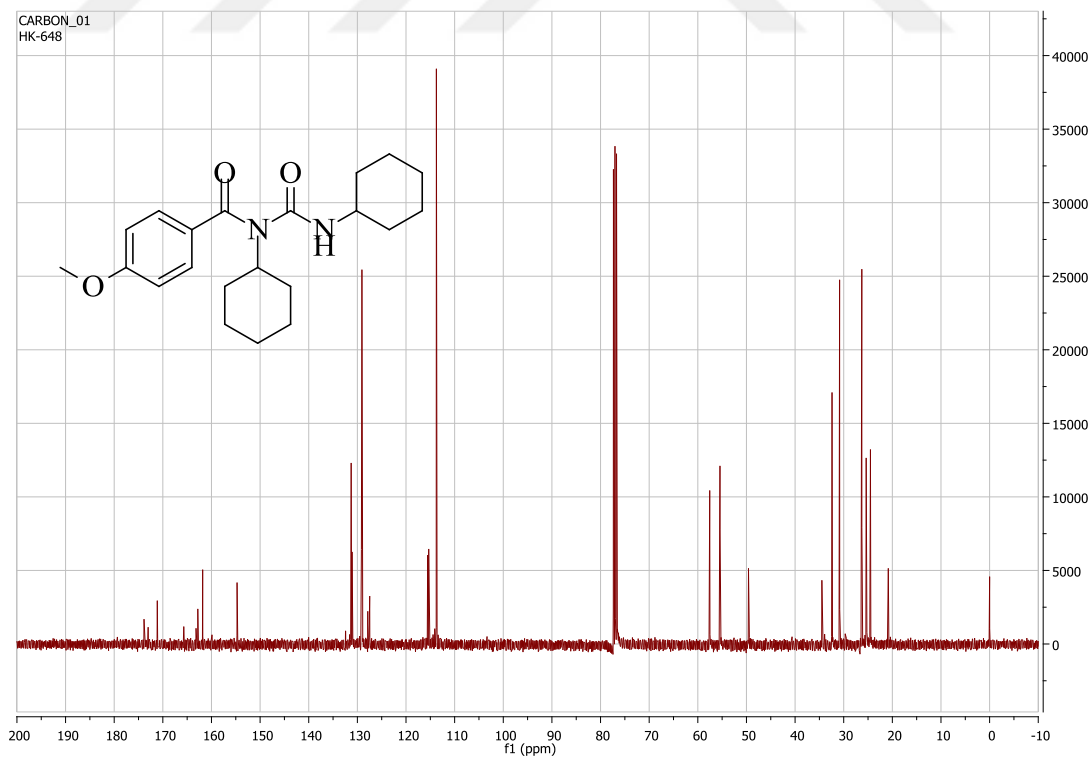


Figure A.166 ¹³C NMR Spectrum of compound 214c

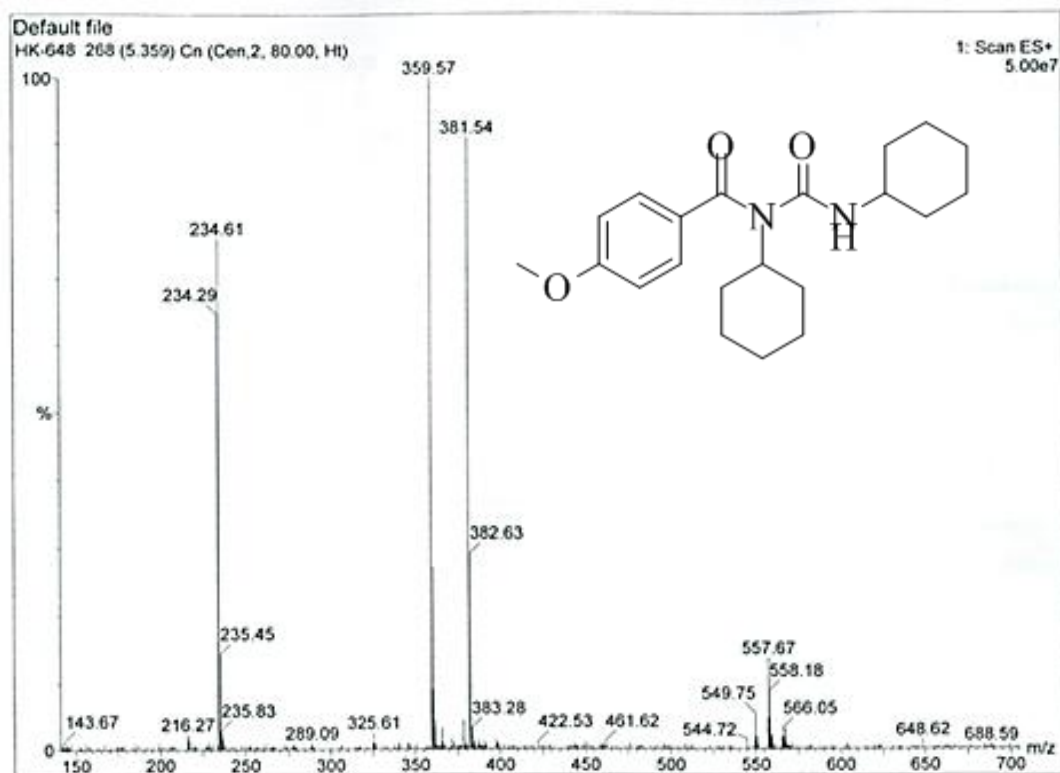


Figure A.167 MASS Spectrum of compound 214c

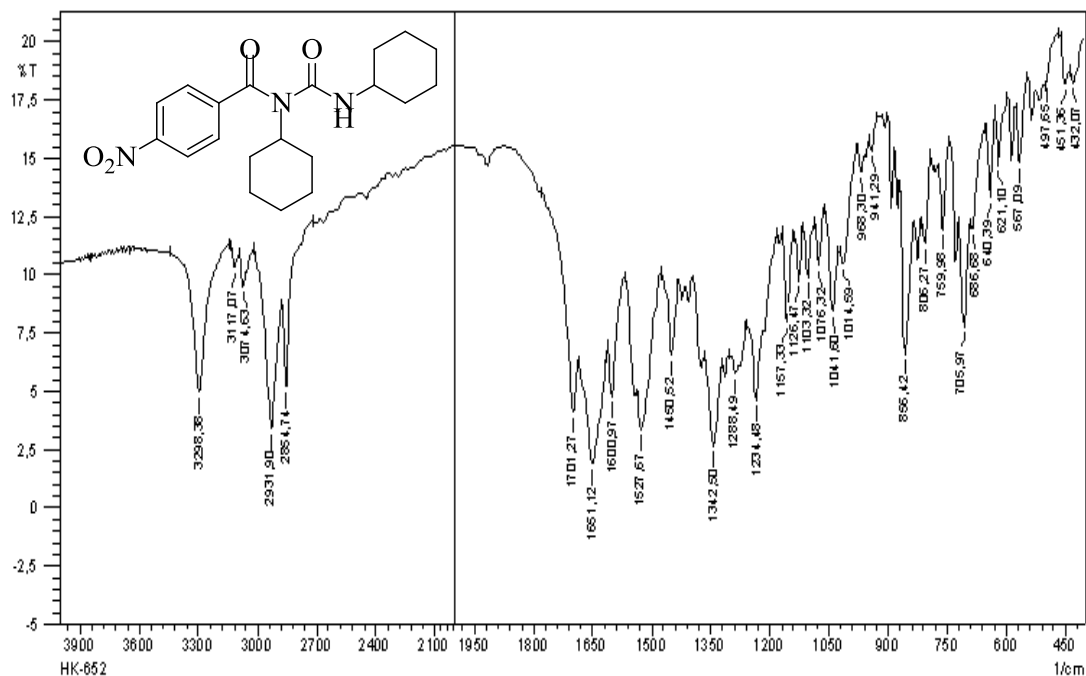


Figure A.168 IR Spectrum of compound 214d

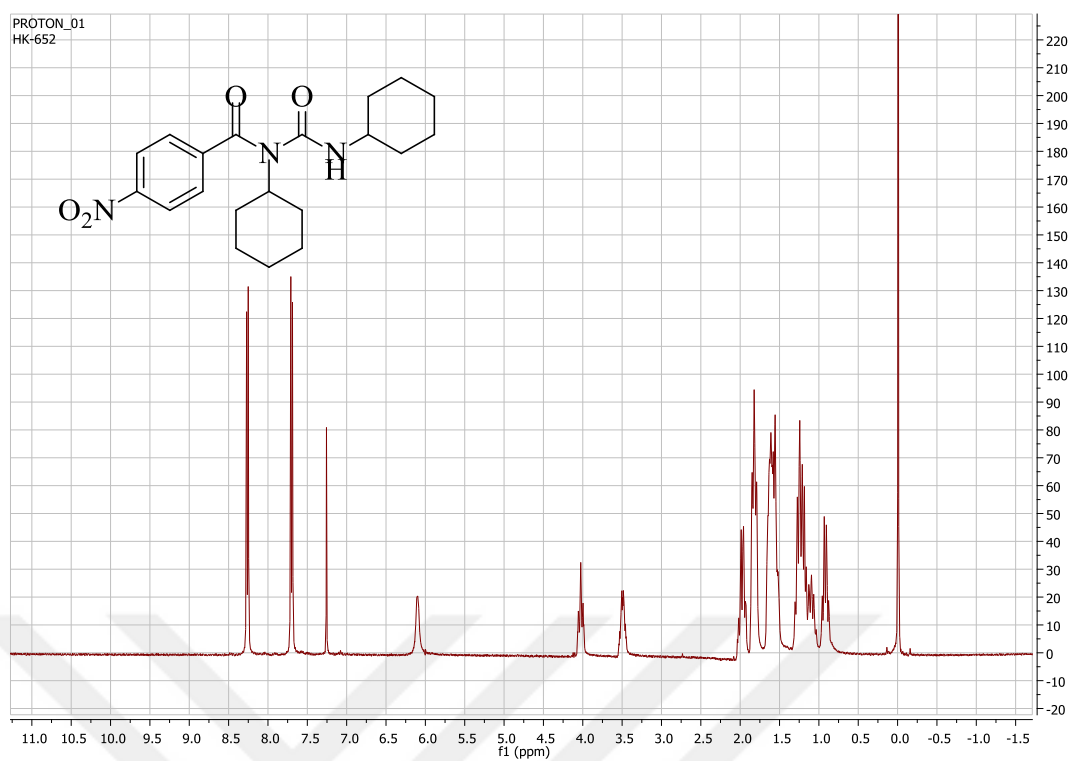


Figure A.169 ¹H NMR Spectrum of compound **214d**

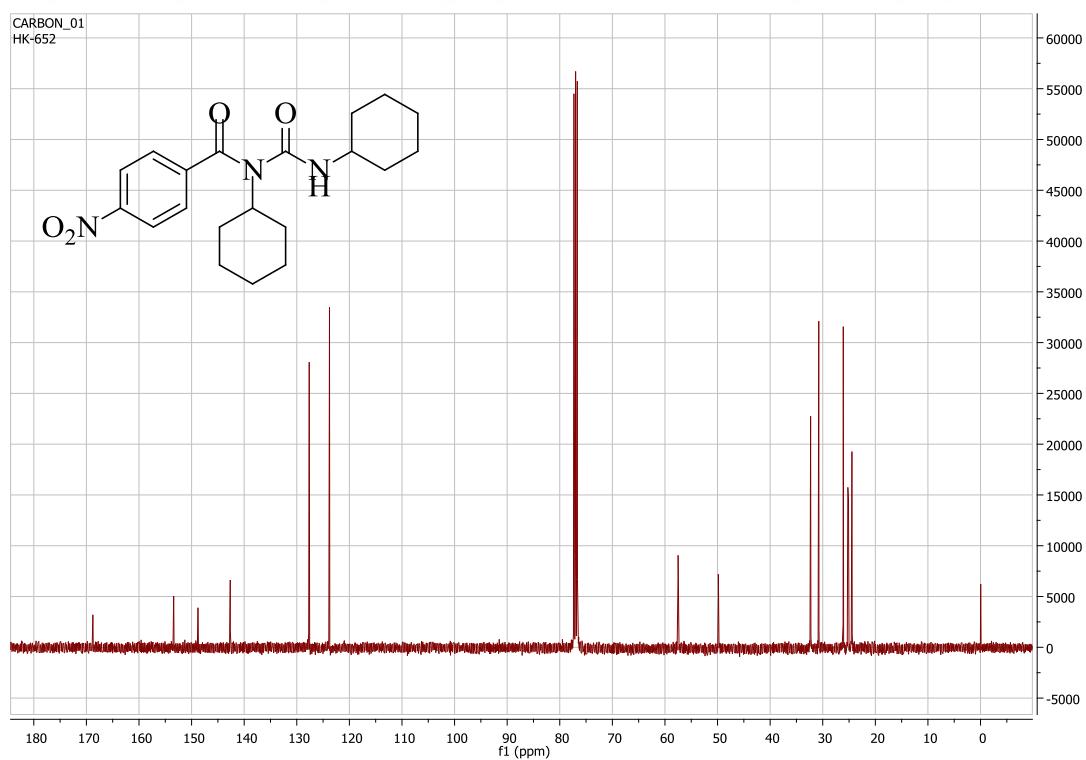


Figure A.170 ¹³C NMR Spectrum of compound **214d**

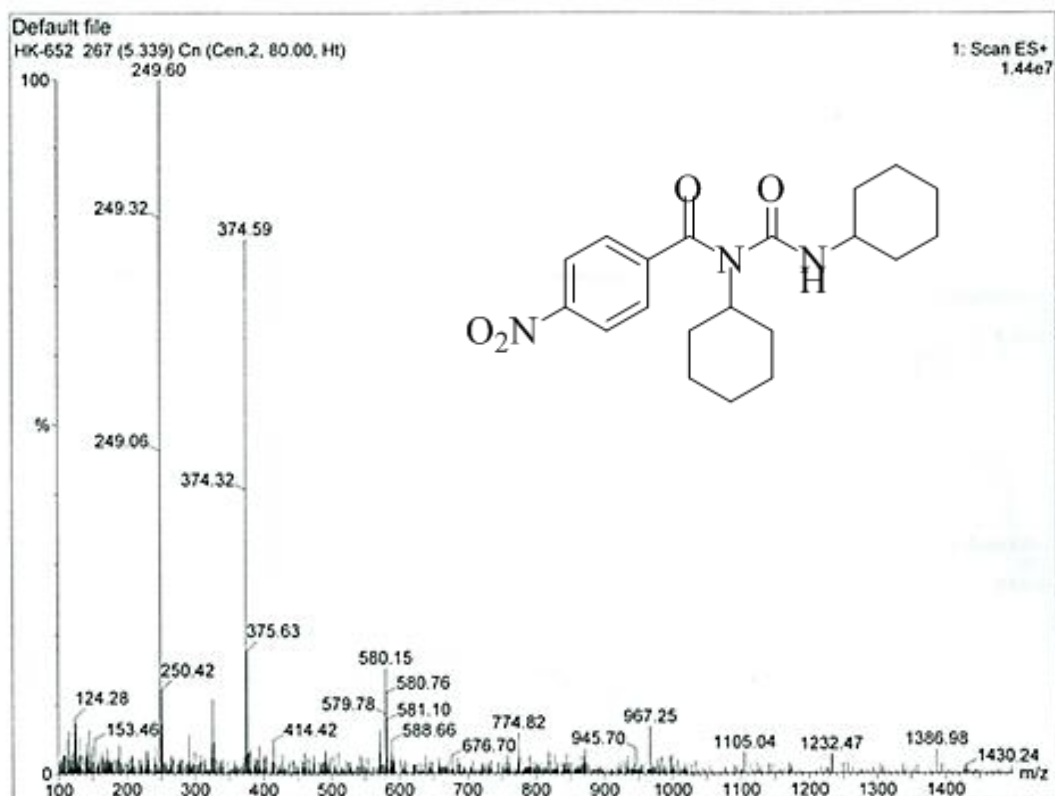


Figure A.171 MASS Spectrum of compound 214d

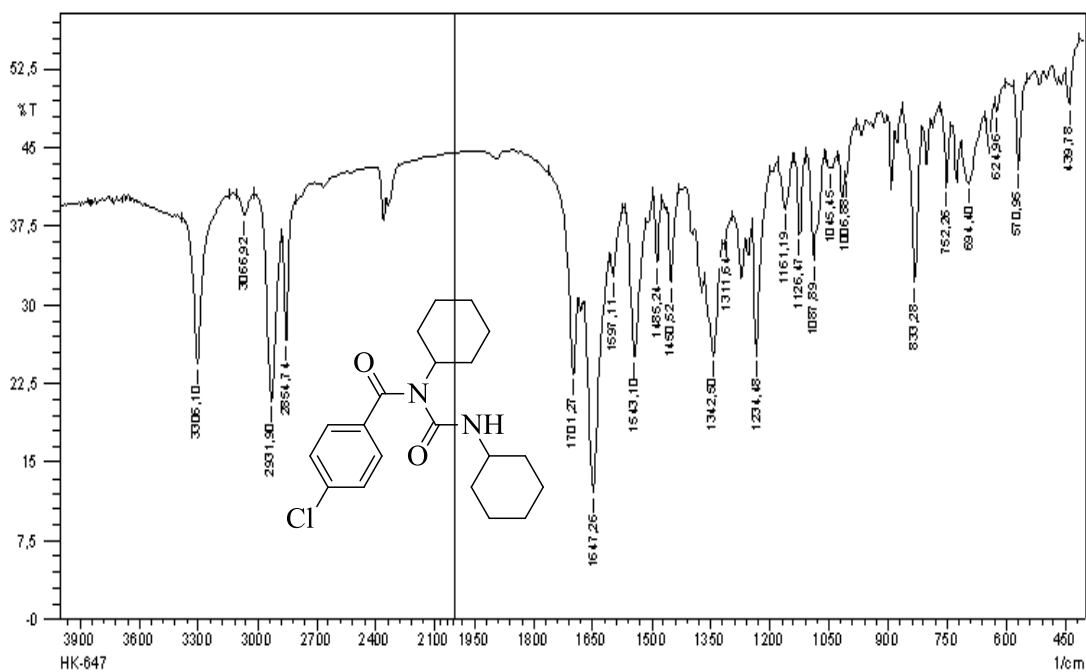


Figure A.172 IR Spectrum of compound 214e

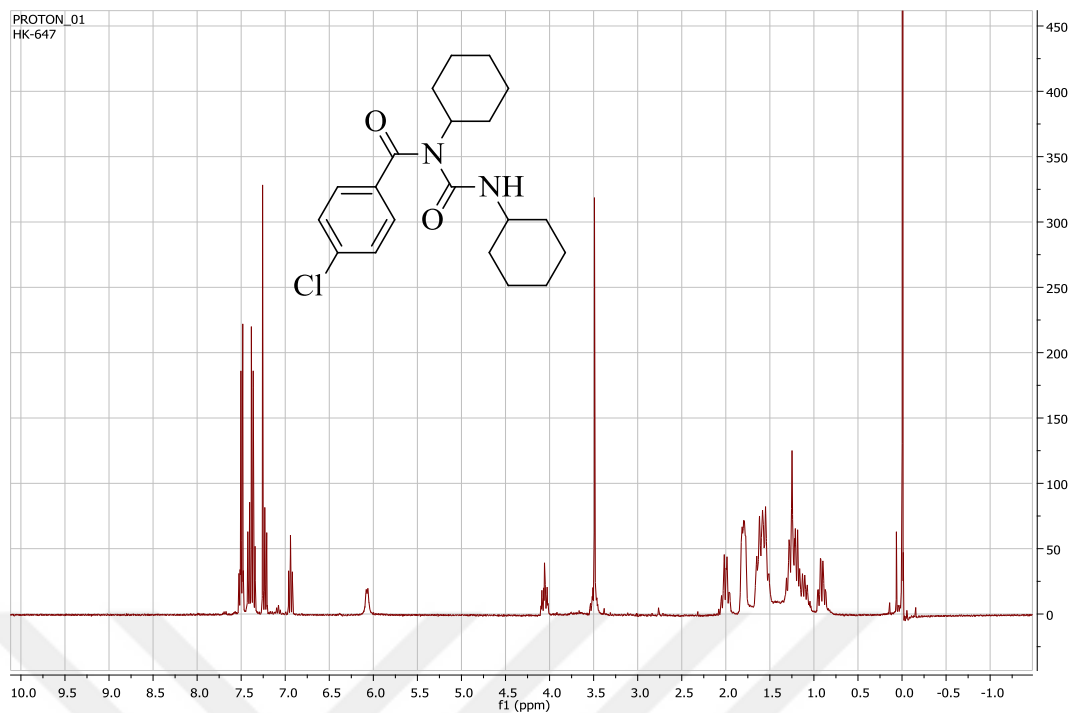


Figure A.173 ¹H NMR Spectrum of compound 214e

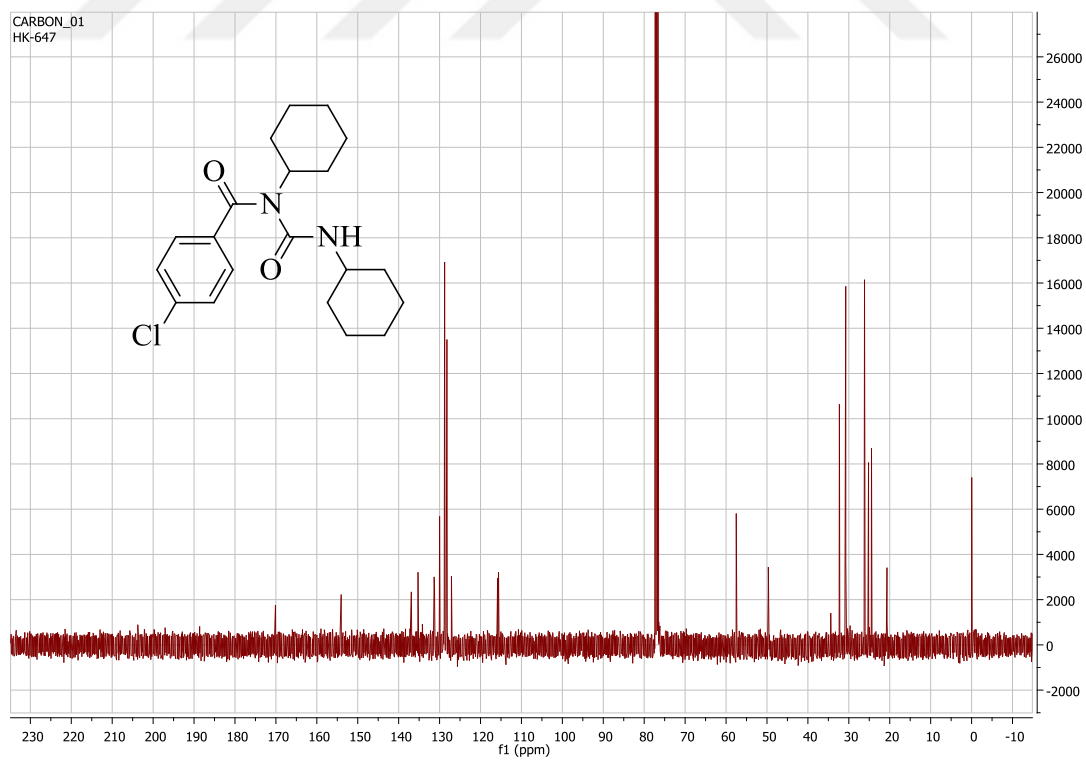


Figure A.174 ¹³C NMR Spectrum of compound 214e

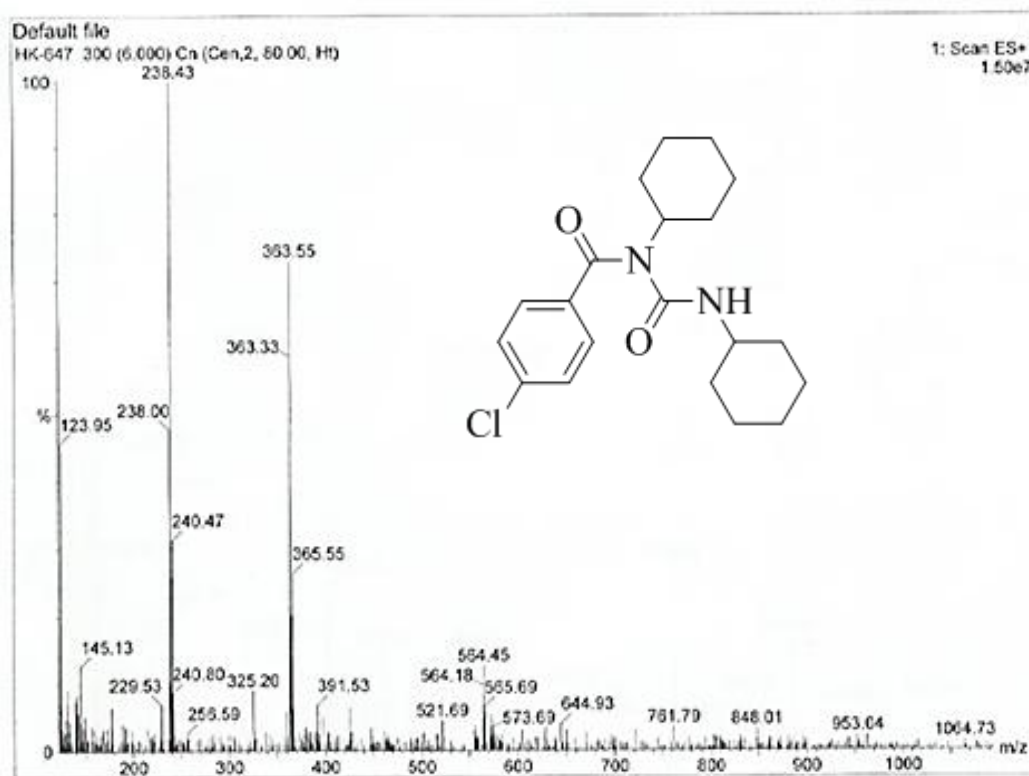


Figure A.175 MASS Spectrum of compound 214e

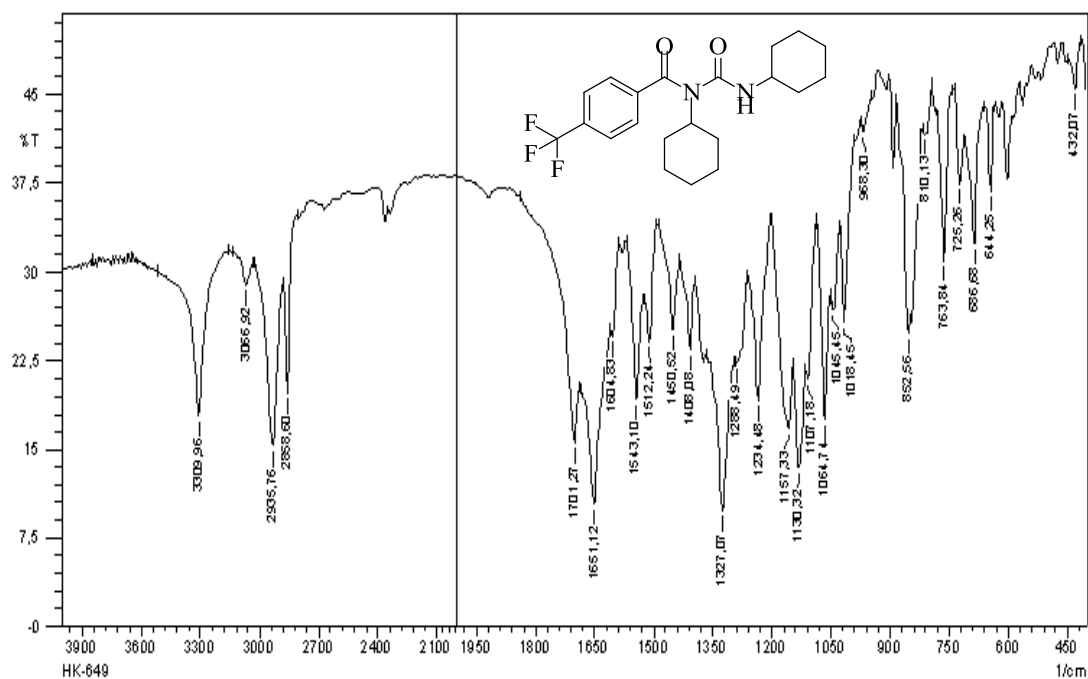


Figure A.176 IR Spectrum of compound 214f

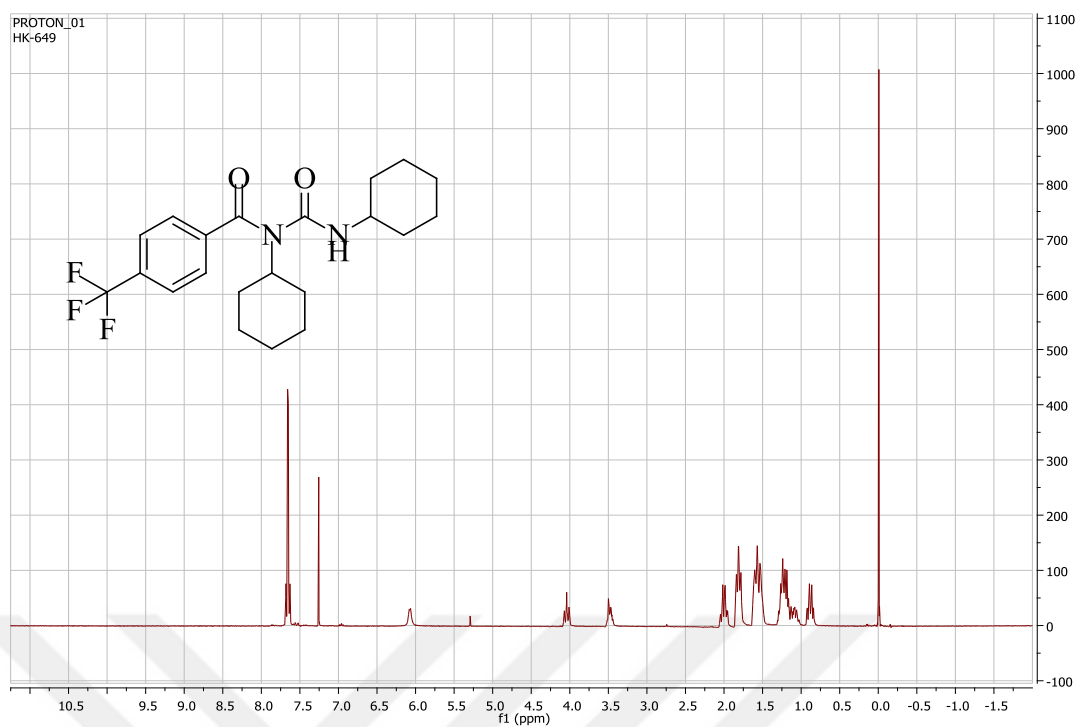


Figure A.177 ^1H NMR Spectrum of compound 214f

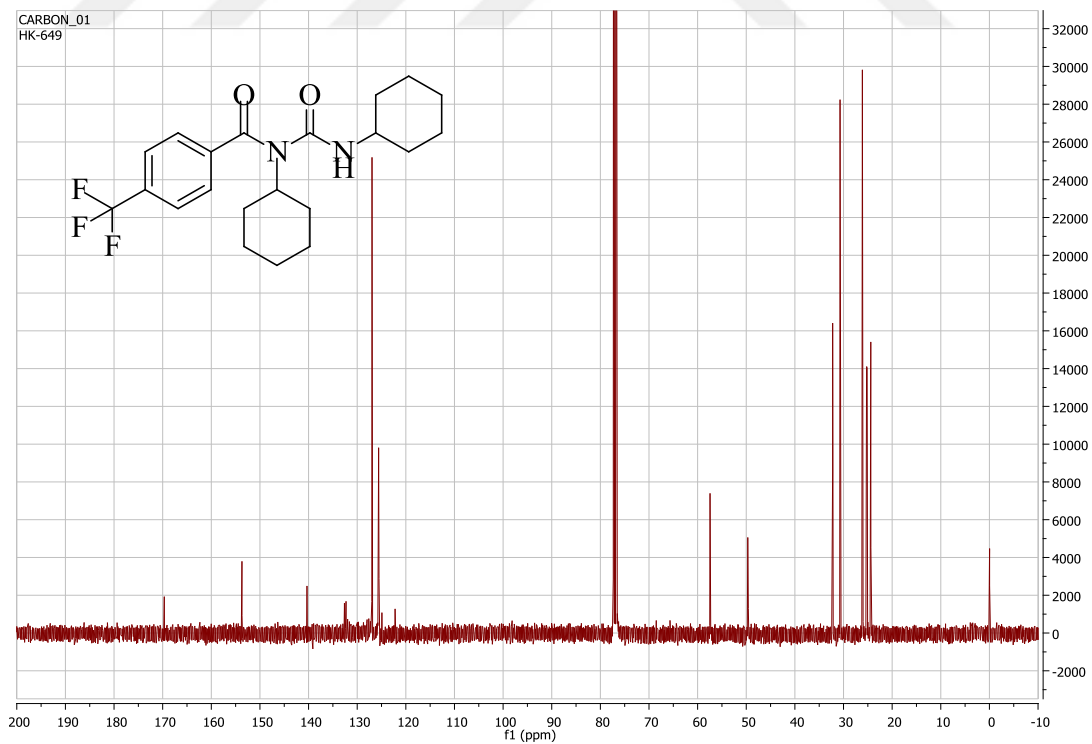


Figure A.178 ^{13}C NMR Spectrum of compound 214f

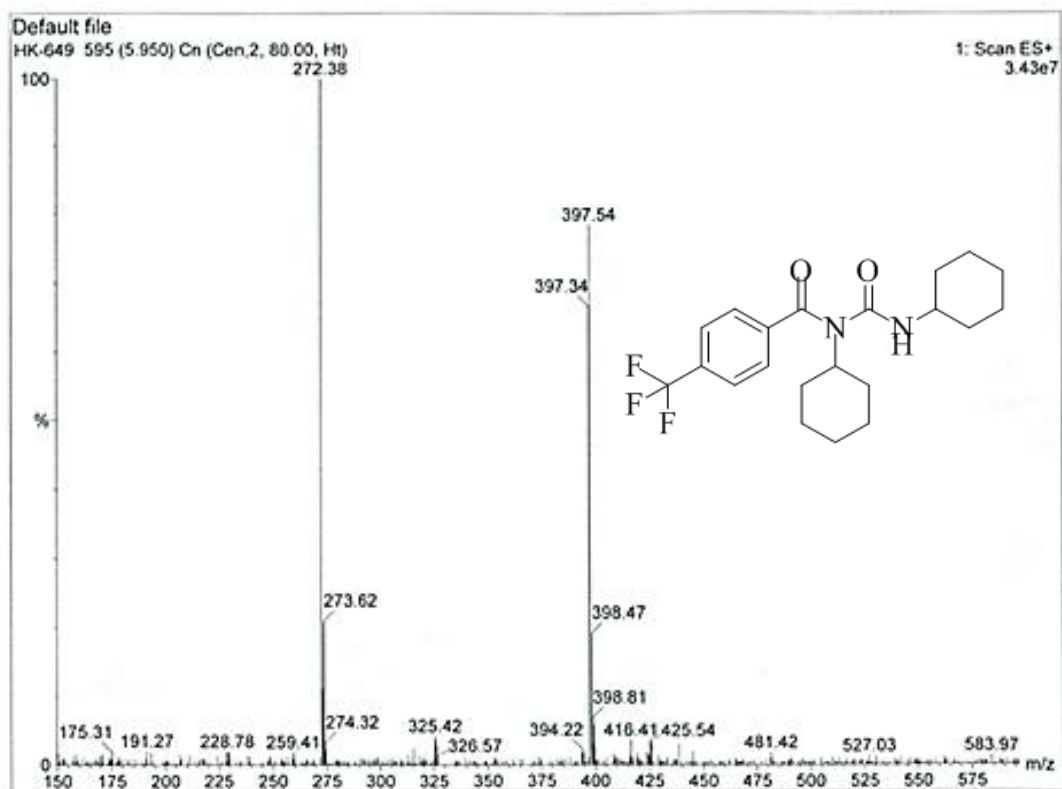


Figure A 179 MASS Spectrum of compound 214f

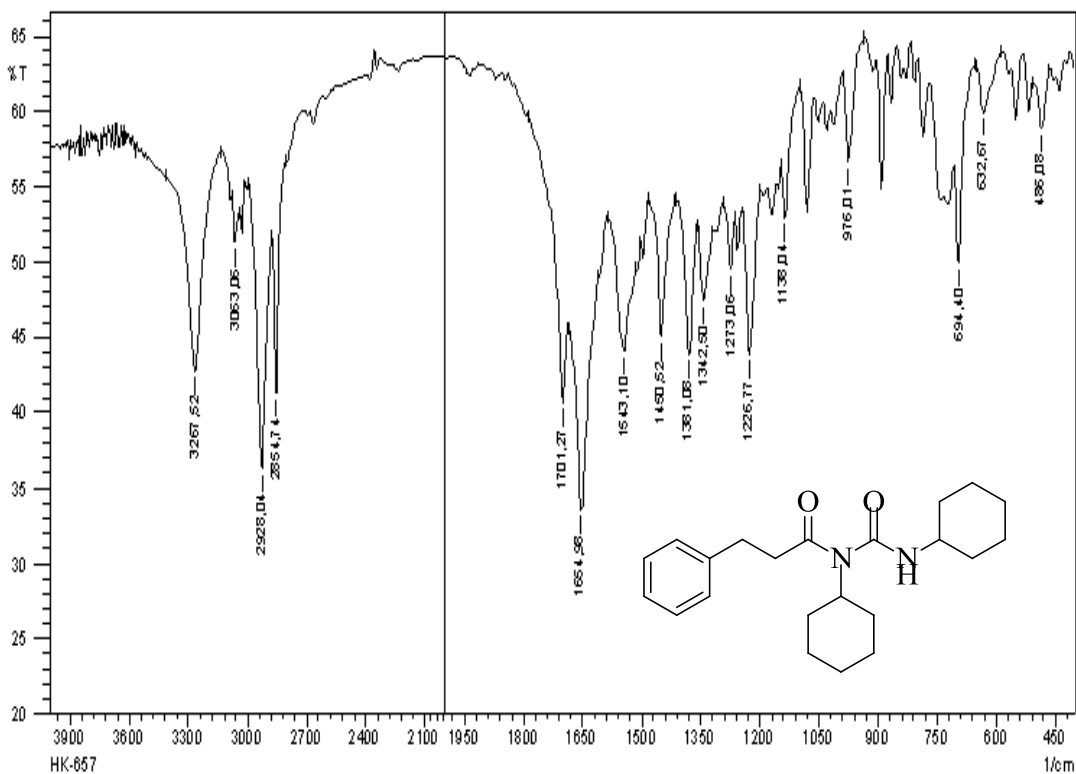


Figure A.180 IR Spectrum of compound 214g

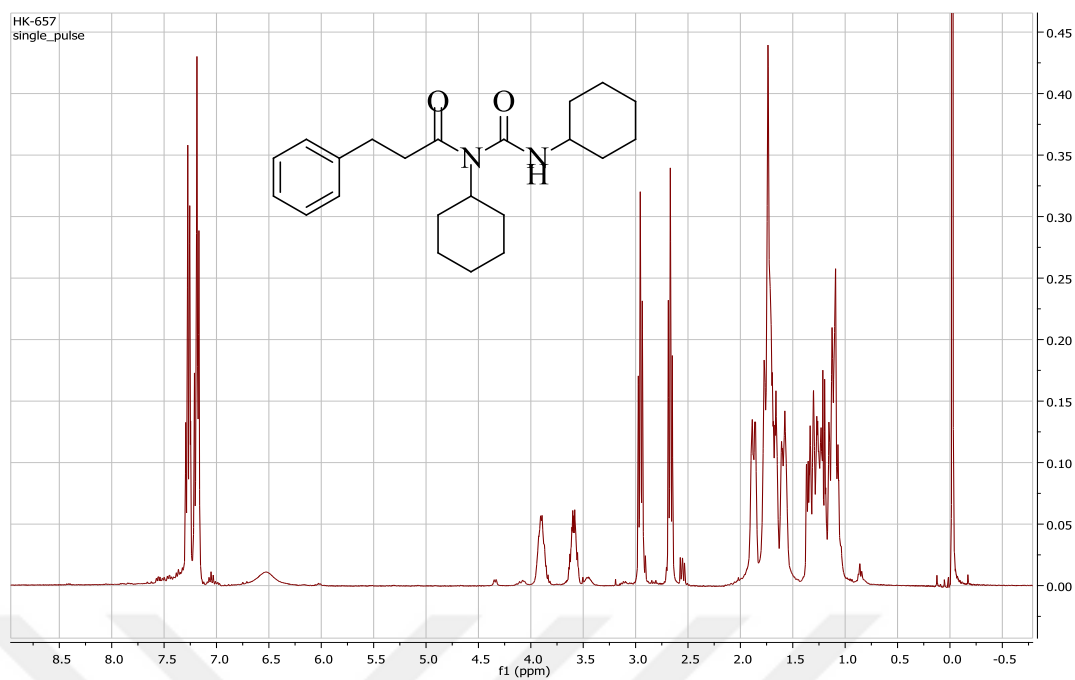


Figure A.181 ^1H NMR Spectrum of compound 214g

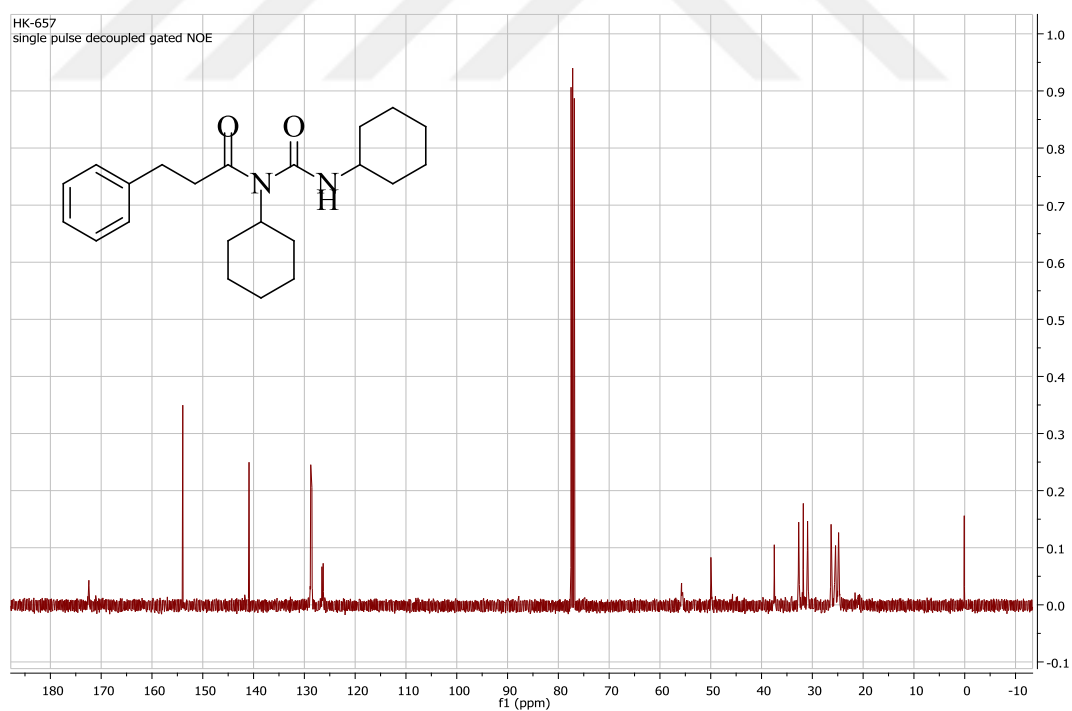


Figure A.182 ^{13}C NMR Spectrum of compound 214g

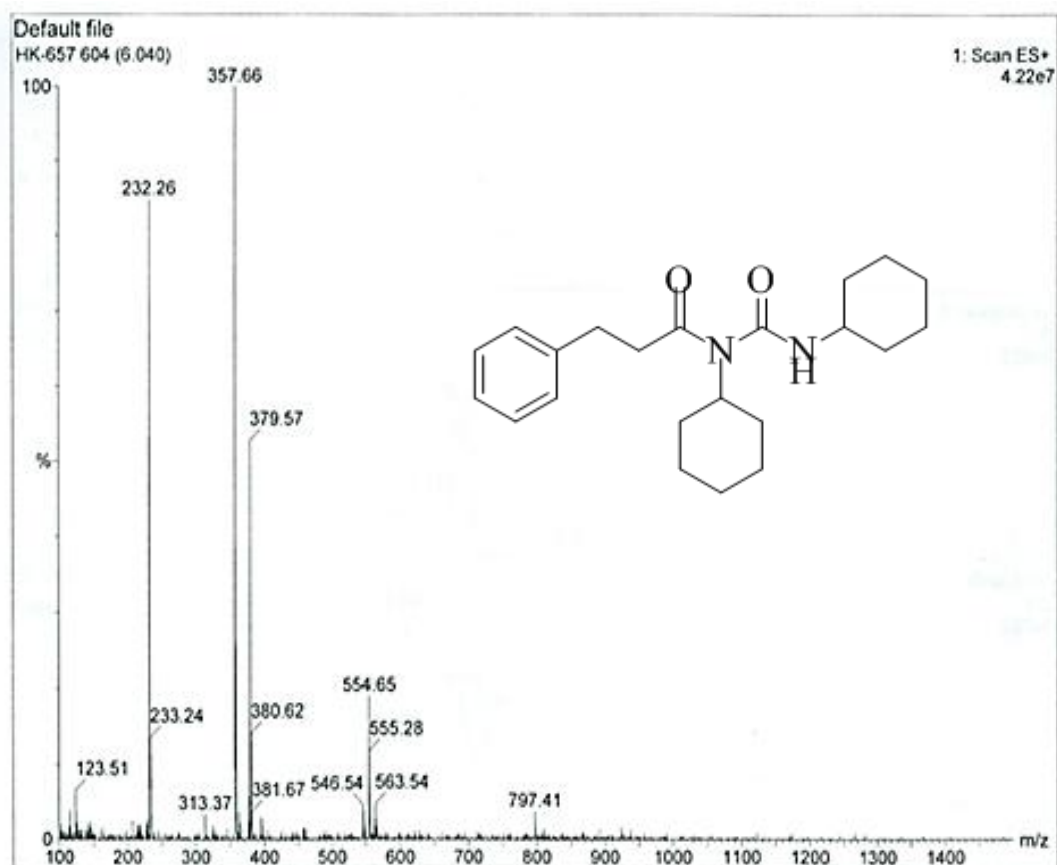


Figure A.183 MASS Spectrum of compound 214g

8. CURRICULUM VITAE

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2003-2008	Abant İzzet Baysal University Faculty of Sciences Department of Chemistry-BSc Degree (English)
1999-2003	İbrahim Turhan High School (İstanbul)

Communications to scientific meetings

H. Karakuş, Y. Dürüst, Synthesis of Novel Azides Bearing 1,2,4-Oxadiazole and 1,3-Dipolar Cycloaddition Reactions with *N*-phenylmaleimide. 24. National Chemistry Congress, 29 June-2 July 2010, Zonguldak, TURKEY.

H. Karakuş, Y. Dürüst, Synthesis of Novel Triazoles Bearing 1,2,4-Oxadiazole Ring. Current Topics in Organic Chemistry, 6th-10th June 2011, Novosibirsk, RUSSIA.

M.Yıldırım, H.Karakuş, David W.Knight, Electrophile-catalyzed Cascade Cyclisation of Geranyl Sulfonamide and Carbamate Derivatives. IUPAC-44TH World Chemistry Congress, 11-16th August 2013, İstanbul, TURKEY.

H. Karakuş, Y. Dürüst, Microwave-Assisted Cycloaddition Reaction of Münchnones with Benzo[b]thiophene 1,1-dioxide. Anatolian Conference on Synthetic Organic Chemistry (ACSOC), 16th-19th March 2015, Antalya, TURKEY.

H. Karakuş, Y. Dürüst, Dakin-West Type Reactions of 2-(4-Substitutedphenyl)-2-(*N*-Methyl-*N-p*-Substitutedbenzamido)acetic Acids in the Presence of 2-Nitromethylene thiazolidine. Anatolian Conference on Synthetic Organic Chemistry (ACSOC), 16th-19th March 2015, Antalya, TURKEY.

Publications

Y. Dürüst, H. Karakuş, M. Kaiser, D. Tasdemir. Synthesis and anti-protozoal activity of novel dihydropyrrolo [3,4-*d*][1,2,3]triazoles, EUR. J.MED. CHEM., 48, 296-304 (2012).

Y. Dürüst, H. Karakuş, M. Z. Yavuz, A. A. Gepdiremen, Synthesis of novel triazoles bearing 1,2,4-oxadiazole and phenylsulfonyl groups by 1,3-dipolar cycloaddition of some organic azides and their biological activities, TURK. J. CHEM. 38, 739-755 (2014).